

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
17-970/S-046**

**Correspondence**

# FAX



**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

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**To:** Laura Garcia Davenport, Zeneca

**From:** Amy Baird, CSO

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**Fax:** 302-886-2822

**Fax:** (301) 594-0498

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**Phone:** 302-886-7533

**Phone:** (301) 594-5771

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**Pages, including cover sheet:** 2

**Date:** 6-28-00

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**Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate).**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

**COMMENTS:**

Please commit to the following Phase 4 requests..see attached. Please do not hesitate to call should you have any questions.

Thank you,

  
Amy Baird

1. Please commit to address, in a labeling supplement, issues conveyed to you on June 22, 2000, regarding the Geriatric Use section of the labeling. The labeling supplement must be submitted to the Agency 3 months from the date of the approval of this supplement.
2. Please commit to address, in a labeling supplement, issues conveyed to you in FDA facsimiles dated June 28, 2000, regarding pharmacology/toxicology and biopharmaceutical sections of the labeling. The labeling supplement must be submitted to the Agency 3 months from the date of the approval of this supplement.

**APPEARS THIS WAY  
ON ORIGINAL**



SENT VIA RAPIFAX  
AND UPS NEXT DAY AIR

JUN 29 2000

Dr. Richard Pazdur  
Division Director  
Division of Oncologic Drug Products  
Food and Drug Administration  
HFD No. 150, Room No. 2055  
Woodmont II Building  
1451 Rockville Pike  
Rockville, MD 20852-1448

ATTN: 3rd Floor Documentation Room

Dear Dr. Pazdur:

RE: NOLVADEX<sup>®</sup> (tamoxifen citrate)  
NDA 17-970/S-046

Response to FDA Request for Phase IV Commitment - NOLVADEX DCIS

Reference is made to the Agency's facsimiles of June 28, 2000, in which the Agency provided labeling comments from the Pharmacology/Toxicology and Biopharmaceutical teams. Reference is also made to the Agency's facsimile of June 28, 2000, in which the Agency requested Phase IV commitments to address these comments in the labeling, as well as the June 22, 2000 request to include a B-24 Geriatric Use section for NOLVADEX<sup>®</sup> (tamoxifen citrate) DCIS sNDA submission of December 29, 1999.

The purpose of this submission is to provide a response to the Agency. For clarity, the Agency's Phase IV commitments are provided below in bold type followed by AstraZeneca Pharmaceuticals LP's (AstraZeneca) response.

- 1. Please commit to address, in a labeling supplement, issues conveyed to you on June 22, 2000, regarding the Geriatric Use section of the labeling. The labeling supplement must be submitted to the Agency 3 months from the date of the approval of this supplement.**

AstraZeneca hereby agrees to revise the labeling to address the clinical comment regarding the Geriatric Use section of the labeling within three months of the approval date for the DCIS indication.

- 2 -

2. Please commit to address, in a labeling supplement, issues conveyed to you in FDA facsimiles dated June 28, 2000, regarding pharmacology/toxicology and biopharmaceutical sections of the labeling. This labeling supplement must be submitted to the Agency 3 months from the date of the approval of this supplement.

AstraZeneca hereby agrees to revise the labeling to address the pharmacology/toxicology and biopharmaceutical comments within three months of the approval date for the DCIS indication.

Please do not hesitate to contact me if there are any questions or concerns regarding this submission.

Sincerely,



Laura E. Garcia-Davenport, M.S.

Senior Product Manager

Regulatory Affairs Department

(302) 886-7533

(302) 886-2822 (fax)

LGD/SLR/tbm

Desk Copies: Ms. Amy Baird, HFD No. 150, Room No. 2106  
Ms. Joyce Mull, MPM, Four Allegheny Center, 5<sup>th</sup> Floor

# FAX



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**From:** Amy Baird, CSO

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**Date:** 6-27-00

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**Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate).**

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## COMMENTS:

In regards to your facsimile of 6-26-00 which provided proposed language for the Geriatric Use section of the labeling:

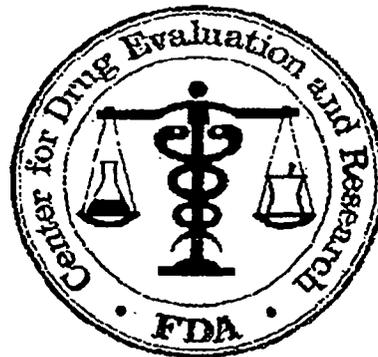
**Draft**

Please also provide a statement regarding efficacy for women < 65 and > 65...similar to that done for the P-1 trial.

Thank you,

  
Amy Baird

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**Date:** 6-21-00

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**Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate).**

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**COMMENTS:**

See the attached request from biopharm for information. Please do not hesitate to call should you have any questions.

Thank you,

  
Amy Baird

CC: Div. NDA 17-970/S-046  
HFD-150 / Div. File  
HFD-150 / Baird

Please provide information regarding what studies were used as the basis for the following statement in the package insert:

**PRECAUTIONS**

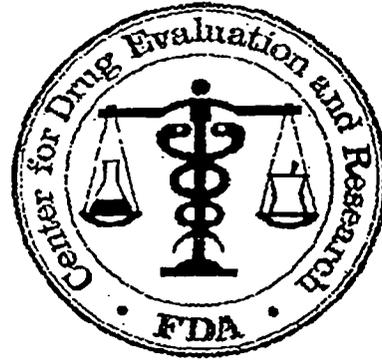
**Drug Interactions**

“...tamoxifen, N-desmethyl tamoxifen and 4-hydroxytamoxifen have been found to be potent inhibitors of hepatic cytochrome p-450 mixed function oxidases. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known.”

**APPEARS THIS WAY  
ON ORIGINAL**

# FAX

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5600 Fishers Lane, Rockville, MD 20857



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**From:** Amy Baird, CSO

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**Pages, including cover sheet:** 5

**Date:** 6-6-00

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**Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate).**

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## COMMENTS:

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

  
Amy Baird

CC: Orig. NDA 17-970 / 5041  
HFD-150 / Div. File  
HFD-150 / Baird

1. The electronic database lists the following patients as having had superficial phlebitis, but the CRFs for these patients were not submitted:

440972058  
444285935  
442018201

CRFs for other patients with superficial phlebitis were included as part of the sNDA. Why were the CRFs for these patients not included? Please submit these CRFs for review ASAP.

2. The electronic database includes multiple CTC codes for neurologic events. In reviewing these events, it is difficult to determine which of these patients may or may not have had strokes. If one excludes neuro-headache (which in most cases is probably unrelated to a serious neurologic event) and neuro-vision (which might be a symptom of a stroke/TIA, but most commonly represents unrelated complaints), there are still 89 unique patients with neurologic complaints. Only CRFs for patients with stroke as determined by NSABP were submitted. Please document how stroke cases were assigned.

TRT	SN
1	440085298
1	440187200
1	440196318
1	440418118
1	440737375
1	440770290
1	440799248
1	440872298
1	440963337
1	441104318
1	441330247
1	441436197
1	441625165
1	441643225
1	441652137
1	441849290
1	442017289
1	442102124
1	442322290
1	442335200
1	442513348
1	442544269
1	442612491
1	442617936
1	442655913
1	442675907
1	442834091
1	442952913

1 442955247  
1 442996247  
1 443069416  
1 443079225  
1 443163925  
1 444044936  
1 444188297  
1 444207949  
1 444241271  
1 444721201  
1 444792158  
1 444923244  
1 444952290  
2 440150023  
2 440244291  
2 440274247  
2 440303912  
2 440449297  
2 440677014  
2 440868290  
2 440882201  
2 440980903  
2 441144159  
2 441179415  
2 441329182  
2 441447014  
2 441514171  
2 441526942  
2 441622925  
2 441704903  
2 441922201  
2 441929925  
2 441952926  
2 441979223  
2 442003951  
2 442061311  
2 442097065  
2 442228231  
2 442346145  
2 442658231  
2 442737375  
2 442820336  
2 442823344  
2 442879022  
2 443144022  
2 443290171  
2 443652361

2 443787928  
2 443855247  
2 443863171  
2 443899214  
2 443902201  
2 444017931  
2 444180247  
2 444294247  
2 444368197  
2 444604376  
2 444631200  
2 444697108  
2 444703271  
2 444928290

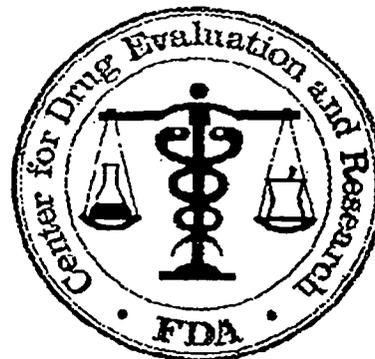
3. Please define which IDC codes were used in table ALLADR for OCOD1-4.
4. Please define "OTHER toxicity 1 and 2" (OTHR1, OTHR2) and OTHR1 and OTHR2. What toxicities do these categories refer to?
5. Twenty-four patients complained of various pulmonary symptoms during the course of the study. Were the CRFs of these patients reviewed to ensure that pulmonary emboli were not underreported?

TRT	SN
1	440196318
1	440974247
1	441440290
1	441814947
1	442053960
1	442165301
1	442952913
1	443069416
1	443322296
1	444188297
1	444241271
1	444599250
1	444879200
2	440244291
2	440772250
2	441559960
2	441629940
2	441664171
2	441897906
2	442271928
2	443656290
3	443732301

2 444180247  
2 444356199

APPEARS THIS WAY  
ON ORIGINAL

# FAX



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5600 Fishers Lane, Rockville, MD 20857

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**To:** Laura Garcia Davenport, Zeneca

**From:** Amy Baird, CSO

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**Fax:** 302-886-2822

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**Phone:** 302-886-7533

**Phone:** (301) 594-5771

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**Pages, including cover sheet:** 2

**Date:** 5-30-00

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**Re:** NDA 17-970/S-046<sup>46</sup>. Specifically, your submission dated June 24, 1999.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

## COMMENTS:

See the attached post-approval request for a commitment. Please do not hesitate to call should you have any questions.

Thank you,

  
Amy Baird

cc: Orig. NDA 17-970  
HFD-150 / Div. File  
HFD-150 / Baird

Available data are not adequate to support the requested shelf-life of . . . months for the 180 tablets bottle and 2,500 tablets bottles of the 10 mg strength, and the 90 tablets and 1,250 tablets bottles of the 20 mg strength. Our statistics consult has concluded that given the sparse stability data of 10 mg 2,500 tablets, 20 mg 90 tablets and 20 mg 1,250 tablets presentations, regression analyses can not be performed. We would like to have your post-approval commitment to initiate a stability study to establish the stability profiles of the 180-count and 2,500-count presentations of the 10 mg strength and the 90-count and 1,250-count presentations of the 20 mg strength. A bracketing design of study protocol may be used, however, the protocol should be submitted for approval first.

**APPEARS THIS WAY  
ON ORIGINAL**

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Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

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To: Laura Garcia Davenport, Zeneca

From: Amy Baird, CSO

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Pages, including cover sheet: 1

Date: 5-17-00

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Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate).

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## COMMENTS:

See the following clinical comment. Please do not hesitate to call should you have any questions.

Although you state that the CRF for patient 442033906 is located in volume 156, it is not present in the Agency volume identified as volume 156. Please send another copy of this patient's CRF as soon as possible.

Thank you,

Amy Baird

CC: Dug. I NDA 17-970/504  
HFD-150 / Dir. File  
HFD-150 / Baird

# FAX



**FOOD AND DRUG ADMINISTRATION  
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**From:** Amy Baird, CSO

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**Pages, including cover sheet:** 1

**Date:** 5-17-00

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**Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate).**

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**COMMENTS:**

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

0  
15/1  
Amy Baird

CC: Orig. NDA 17-970/S-046  
HFD-150 / Div. Files  
HFD-150 / Baird

1. Please provide the baseline mammogram reports for patients 441408109 and 444023066, which are not present in the CRFs. Also, please supply a bilateral baseline mammogram report for patient 442028086; only an ipsilateral report is present in the CRF.
2. The CRF for patient 442036017 does not contain the pathology reports for the original lesion. A physician note mentions that microinvasion was present on at least one reading by a consultative pathologist. Please provide the pathology reports for review.
3. Patient 440406112 had an ipsilateral recurrence first diagnosed as DCIS on biopsy, but definitive procedure (mastectomy) showed invasive cancer. Please clarify why this patient was classified as having a non-invasive event.
4. Patient 444708950 had a series of abnormal spine films in 1996. It is not clear from the reports whether she was considered to have metastatic disease or osteoporosis. Did she have a bone biopsy? Are further follow-up data available to clarify this issue?
5. Patient 443929926 volume 88, page 238: pathology report notes "multifocal DCIS with focal areas suggesting early stromal invasion." Please clarify why this patient was classified as having an ipsilateral non-invasive rather than invasive cancer.
6. Pt 444743357 (volume 89, page 006): please provide the results of surgery for a pelvic mass, planned for April 1999.
7. Pt 443156354, volume 90, page 016: noted to have an irregular density in the right breast on mammogram 3/6/96. Recommended to have a 6-month mammogram. Please provide the follow-up mammogram report and verify whether the patient subsequently developed another breast recurrence.
8. Patient 440047014, volume 93, page 23: The note indicates that she had an abnormal contralateral mammogram and was advised to undergo a biopsy in March or April 1996. Please provide the pathology report of this procedure.
9. Pt 440805207, vol 150: The patient had an FNA on a breast lesion on 9/25/95, reported to look like a lipoma on ultrasound. Please submit the pathology report for this procedure.
10. Pt 440846415, vol 150: Pages 238-243 report grade 2 vaginal bleeding and severe cramps. On page 244, the event is recorded as grade 3, and the note indicates that biopsy reports, doctor's notes, an op report and discharge summary were submitted. These documents are not included in our copy of the CRF. Please submit them for review.
11. Pt 1008270, volume 151: please submit the pathology reports of the endometrial biopsy (1/9/96) and fibroid resection (1/31/96) referred to on page 26 of the CRF.
12. Pt 441661247, volume 153: This postmenopausal patient developed vaginal bleeding and had an endometrial biopsy on 2/16/95 (page 157). Please provide the pathology report.

13. Pt 441807022 was classified as having superficial thrombophlebitis by the NSABP. However, her physicians listed her diagnosis as DVT, admitted her to the hospital, administered heparin, and stopped study drug. Please clarify why she was not classified as having a DVT.
14. Pt 443026240, volume 162: This patient was admitted to the hospital for work-up of hemolytic anemia and was found to have multiple palpable breast nodules (page 13). She was advised to have a work-up. She gave consent for follow-up in 1999. The last mammogram report in the CRF is from 1992. Please provide an update, if available, on her breast cancer status.
15. Pt 44591352, volume 171: Please provide the pathology report from the uterine biopsy performed 2/1/96.
16. Pt 444259187, volume 170: This patient complained of calf pain and shortness of breath and stopped study drug (page 81). Please provide the details of any work-up performed for these symptoms.

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

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**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

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**To:** Gary M. Cooper

**From:** Amy Baird, CSO

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**Fax:** 302-886-2822

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**Phone:** 302-886-5132

**Phone:** (301) 594-5771

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**Pages, including cover sheet:** 2

**Date:** 4-13-00

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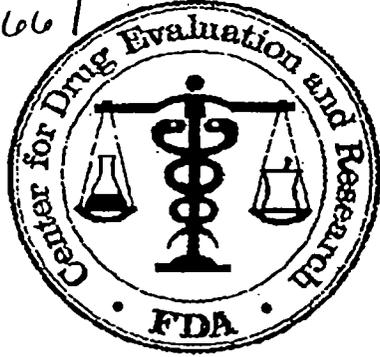
0 /S/ --  
Amy Baird

CC: Orig. NDA 17-970 / 5046  
HFD-150 / Div. File  
HFD-150 / Baird

1. Patient 443539943: volume 21, page 100: The "Other physical findings" indicates that this patient had numbness of the left face and difficulty moving her lips. Can you provide additional documentation that supports the conclusion that these findings are secondary to an old Bell's palsy rather than to a TIA or stroke? The Bell's palsy is reported to have occurred 35 years previously, and no neurologic symptoms were recorded from randomization to this visit date.
2. Patient 440156187 is reported in volume 20, pages 55 and 96 to have suffered a stroke. Please clarify why she is not included in the list of patients reported to have had a stroke.
3. Patient 442653208 is reported to have had a stroke in volume 23, page 21. Please clarify why she was not coded as having had this event.
4. Subject number 442033906 is listed under Withdrawals due to Adverse Events as DVT grade 3. First, where is her CRF? The master list indicates that it is in volume 156; volume 156 contains subjects 441807022 and 441825290. Secondly, why was this patient not included in the list of patients with thromboembolic events?
5. Patient 443074212 is listed as having had a non-invasive contralateral breast cancer. However her pathology report (volume 111, page 39) reports extensive DCIS with 0.9 cm of invasive cancer. Please clarify why this patient was not instead classified as having a contralateral invasive breast cancer.
6. Patient 440963337 is reported as having lymphoma in volume 115, page 58 and others. Please clarify why she is not included in the list of patients with "Other Second Primary Cancer."
7. Patient 441712066 developed a contralateral invasive breast cancer, T=3 cm; 1 involved node. A note in volume 98 page 116 indicates that she had high-dose chemotherapy with PSCT and IL-2. Was this procedure performed for metastatic disease? Although she was Stage II, she did not have enough involved nodes nor a tumor large enough to ordinarily be considered for transplant.
8. Patient 441765940 is listed as having a contralateral invasive breast cancer. The CRF in volume 104 contains documentation only for a basal cell carcinoma of the skin overlying the breast. Please supply the documentation for the invasive breast cancer.

To: Joyce Mull, NSABP Div File  
FAX: (412) 330-4661

# FAX



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**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
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<b>To:</b> Gary M. Cooper	<b>From:</b> Amy Chapman, CSO
<b>Fax:</b> 302-886-2822	<b>Fax:</b> (301) 594-0498
<b>Phone:</b> 302-886-5132	<b>Phone:</b> (301) 594-5771
<b>Pages, including cover sheet:</b>	<b>Date:</b> 3-14-00

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**COMMENTS:**

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

Amy Chapman

1/5/00

CC: Orig NDA 17-970/S-046  
HFD-150 / Chapman  
HFD-150 / Div. File

(412) 330-4661  
FAX:

1. Patient 443735225 is listed as having an invasive ipsilateral breast cancer, but the pathology report notes only Paget's disease of the nipple/DCIS. Please provide the documentation for classification of this lesion as invasive cancer (same for patient 443793408).
2. Patient 444356199, CRF in volume 14, the discharge note (pages 104-105) indicates that the V/Q scan was interpreted as high probability coumadin. The V/Q report notes the limitations of the test as performed by the patient and mentions that it is consistent with either COPD or PE. Please document why this event was not listed as a PE, given the clinical interpretation of the patient's exam and studies.
3. Patient 442874118. She is listed as NED without recurrence as of 7/15/95. The next note 7/15/96 indicates that she had a right modified radical mastectomy and now has distant mets. Please clarify whether this patient was coded as having an ipsilateral invasive recurrence. If not, please document your rationale.
4. Patient 444400277 entered the study 12/91 with a dx of left-sided DCIS. However, a mammogram dated 10/9/91 indicates suspicious microcalcifications in the right central breast.
  - a. Please indicate whether the patient was considered eligible. [We understand that you have appropriately performed an intent-to-treat analysis of all randomized patients with follow-up.]
  - b. The patient subsequently developed bilateral mammographic abnormalities, had simultaneous biopsies, which demonstrated contralateral DCIS and ipsilateral invasive disease, and then had simultaneous mastectomies. Please provide the rationale for coding this patient as a contralateral non-invasive breast cancer, but not as an ipsilateral invasive breast cancer. [Note: she ultimately died of metastatic breast cancer.]
5. Patient 444868091 is reported to have died of "pseudo-aneurysm". Patient 440490004 is reported to have died of metastatic breast cancer. Please explain why these patients were not included in the electronic database as deaths.
6. Please note that in table CAUSEDTH, you have entered data for patient 443119066 under the number 443119006. Also in the same table, data for patient 444590259 was entered as number 444500259. Please check the other tables—was the incorrect number used consistently for these patients? If so, please submit corrected copies of the electronic database as soon as possible.

7. In the Lancet publication of the NSABP B-24 trial results, Table 2 does not list cumulative incidence for all contralateral breast cancers. However, the text on page 1997, 2<sup>nd</sup> paragraph states that "the cumulative incidence of all contralateral breast tumors occurring at 5 years as first events was 3.4% in the placebo group and 2.0% in the tamoxifen group." Do these numbers belong in the table, or do they refer to a different calculation? Please clarify.
8. The Briefing Document submitted 5/27/99 (17-970 N064) contains analyses similar to the Lancet publication, but the Technical report submitted as N 072 on 9/30/99 contains slightly different numbers listed in many of the tables. Please verify that the Lancet publication should be used as the best source of data. Please clarify whether the discrepancies are due to different data lock dates.
9. In Table 5, n 072, 22 second cancers (excluding breast and uterus) were reported for women on placebo and 21 for women on tamoxifen. The Lancet publication reports 26 and 25 respectively. Please clarify the discrepancy in these reports and update Table 5 accordingly with the specific types of cancers found.
10. In the Lancet publication, page 1997, second column, first paragraph, the authors state "Ten patients had tumor other than in the breast...". Please clarify the meaning of this paragraph. Do these tumors represent recurrent disease/new primary? If so, how were these patients categorized? However, further in this paragraph, the authors state "These 10 patients were eligible for the trial...". Do these non-breast tumors refer to events prior to study entry? Please describe the diagnoses and findings in these patients.
11. The Lancet publication reports that 564 patients discontinued therapy because of adverse events, personal reasons, and unspecified reasons. The technical document, N 072, page 8 (bottom numbering listed 661 patients as discontinuing early. The sNDA listings in volume 140.2 indicate that 596 patients discontinued early. Please explain the discrepancy between these numbers, and indicate which is the correct number by treatment arm.
12. Please submit the electronic dataset that contains the elements reported on "NSABP B-24 supplemental form for IBTR".
13. The NSABP stated in the pre-sNDA meeting that investigators were not required to report the details of a breast cancer event. However, the protocol indicates that although further treatment was at the discretion of the investigator, all additional therapy for local, regional, distant or ipsilateral breast tumor recurrence was to be reported to the NSABP Biostatistical Center on a follow-up form. The June 16, 1994 amendment to the protocol also contradicts the statement made at the pre-sNDA meeting. The amendment indicates that information documenting the recurrence, including mammogram reports, films, pathology reports, slides, blocks, and the ER/PR status, was to be submitted to the NSABP. Although accrual was complete by this date, information on many breast cancer events should have been captured. Please explain the discrepancy in these statements. The data should be submitted as soon as possible for review.

14. The protocol indicates that the index lesions will be centrally reviewed by the NSABP. The "Analysis for Primary Publication" submitted as N 072 (page 4 of the manuscript) also states that central pathology review will be performed. What is the status of this central review? Please forward results of the review to the Agency.
15. On page 7 of the "Analysis for Primary Publication" (N 072), the authors state "Age was weakly associated with an increased incidence of contralateral tumors, consistent with its well-known status as a breast cancer risk factor." A similar statement does not appear in the Lancet publication. Did age lose its association with contralateral breast tumors with the availability of updated information?
16. Page 7 of the "Analysis for Primary Publication" (N 072) indicates that tumor size was not significantly associated with increased ipsilateral recurrence. The Lance publication does not mention tumor size in association with subsequent events. Was the size of the index lesion analyzed with relation to subsequent events with the dataset used for the Lancet publication and the sNDA submission?
17. Patient 440067089 is listed as having had an invasive ipsilateral breast cancer. In the submitted CRF (volume 38, page 234), the pathology report states "There is no invasive carcinoma." Please indicate whether there is an additional pathology report that documents the presence of invasive cancer.

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# FAX



**FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

<b>To:</b> Gary M. Cooper	<b>From:</b> Amy Chapman, CSO
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<b>Pages, including cover sheet:</b> 2	<b>Date:</b> 2-23-00

**Re: NDA 17-970/S-046. Nolvadex (tamoxifen citrate). Specifically, your submission dated 12-28-99.**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

**COMMENTS:**

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

  
Amy Chapman

CC - Onc . NDA 17-970/S  
HFD-150 Div. File  
HFD-150 / Chapman

**Clinical**

1. With your permission, we would like to send questions simultaneously to the NSABP and to Zeneca in order to shorten the response time. Is this arrangement acceptable to Zeneca?
2. The original NSABP B-24 protocol did not list DCIS versus DCIS mixed with LCIS as a stratification variable for randomization, but this factor was listed in the published report of the trial. When was this change made? How many patients were on study when the change was made? What was the rationale for this change?
3. The sNDA submission contains Appendix B, beginning on page 288 of volume 140.2. This appendix provides minimal information regarding the reasons patients withdrew from study, and does not include the information previously submitted in Table 1, IND [ N 071. Please provide the data in Table 1 in electronic format.

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