CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-541/S-006

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 8-31-00

Re: NDA 20-541/S-006. Arimidex.

COMMENTS:

Please commit to the following Phase 4 commitment. Do not hesitate to call should you have any questions.

To submit annual safety and survival updates for studies 0027 and 0030 until 75% of the patients are deceased.

Thank you,

/S/

Amy Baird

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 8-21-00

Re: NDA 20-541/S-006. Arimidex.

COMMENTS:

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

Thank you,

/S/

Amy Baird

CC: Orig. NDA 20-541/S-006
HFD-150/Div. File
HFD-150/Baird

The FDA queries of the Zeneca databases for studies #27 and #30 give different numbers for thromboembolic disease and vaginal dryness than reported in the Zeneca study reports and in Zeneca's proposed package insert.

The attached Microsoft Access Tables show the FDA's list of patients with these ADRs in study #27 and study #30.

If Zeneca disagrees with the FDA numbers, please provide similar Tables showing Zeneca's list of patients with these ADRs, so the discrepancies can be resolved.

Study #27

	FDA		Zeneca	
	Arimidex	Tam	Arimidex	Tam
Thromboembolic Dis.	11	21	16	24
Vaginal Dry	4	2	7	6

Study #30

	FDA		Zeneca	
	Arimidex	Tam	Arimidex	Tam
Thromboembolic Dis.	8	11	7	15
Vaginal Dry	5	1	8	7

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 8-14-00

Re: NDA 20-541/S-006.

COMMENTS:

See the attached pharmacology comment. **This request for information should be submitted by COB today via facsimile.** Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

cc: Orig. NDA 20-541/S006
HFD-150/Div. File
HFD-150/Baird

The historical control data submitted for the strains used in the carcinogenicity study are not exactly what are needed. Rather than specifying only selective tissues for spontaneous historical control comparison, please submit COMPLETE historical control tissue inventory for benign and malignant lesions for appropriate rat and mouse strains (Wistar and C57B1/10J). Please indicate tissue, tumor, # of animals in which tumor found, total # of animals included in study/sex, total # of lesions and % incidence (optional). Please separate listed tumors by sex of animals.

DN File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 8-14-00

Re: NDA 20-541/S-006.

COMMENTS:

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

Thank you,

/S/

Amy Baird

cc: Orig. NDA 20-541/S-006
HFD-150/Div. File
HFD-150/Baird

In the proposed package insert in Table 6 the subcategories under "Thromboembolic Disease" are less than the total. Please provide the correct numbers and indicate where in the sNDA these numbers can be confirmed.

In the ISS analyses for the effect of age and ethnicity on toxicity were submitted. No comparable analyses were submitted for the effect of age and ethnicity on efficacy. Please submit these analyses.

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 8-1-00

Re: NDA 20-541/S-006.

COMMENTS:

See the attached statistical comment. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

cc: Orig. NDA 20-541/S-006
HFD-150/Div. File
HFD-150/Baird

Results of the FDA's survival analysis for Trials 1033IL/0027 and 1033IL/0030 demonstrate that those patients treated with Arimidex may have inferior survival than those patients treated with Tamoxifen. Since the survival data are premature (cut off date for the survival in the NDA submission is March 10, 1999), the applicant needs to submit the updated survival data (up to June 1, 2000) and the analysis to the agency for review.

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 7-3-00

Re: NDA 20-541/S-006.

COMMENTS:

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

Thank you,

/S/

Amy Baird

cc: Orig. NDA 20-541/S000
HFD-150/Div. File
HFD-150/Baird

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 4-13-00

Re: Arimidex. Specifically, your submission dated 6-10-99. 11-1-99. Also information regarding NDA 20-541/S-006.

COMMENTS:

The pharmacology review of the above noted submission has been completed, see the attached comment. Also, see information regarding NDA 20-541/S-006. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

Orig. NDA 20-541/S-006
HFD-150/Div. File
HFD-150/Chapman

NDA 20-541/S-006

Regarding NDA 20-541/S-006 and the submission of revised labeling

It is acceptable for you to submit revised labeling at this early date in the review period. Per the regulations, a major submission submitted 90 days before (or later) the due date may extend the due date. Please submit the labeling on diskette.

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Chapman, CSO
Fax: 302-886-2822	**Fax:** (301) 827-4590
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 2-9-00

Re: NDA 20-541/S-006. Arimidex (anastrozole). Specifically, your submission dated 11-1-99.

COMMENTS:

Regarding our facsimile of 2-2-00 in which we requested you submit the SAS programs that were used to produce the statistics in Tables ST1-ST199 and Tables ST1-ST205 and your telephone call in which you asked if it would be acceptable if you submitted this requested information in ASCII text. I have discussed this with the statistical reviewer and our information technologist and it is acceptable for you to submit this information in ASCII text. Please see the following comment:

Please send the programs named with an extension of .sas and additionally, please provide documentation (hard copy if possible) indicating which program(s) produces which analysis table.

Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Chapman

CC: Orig. NDA 20-541/S00(
HFD-150/Div. File
HFD-150/Chapman

Div File

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Chapman, CSO
Fax: 302-886-2822	**Fax:** (301) 827-4590
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 2-2-00

Re: NDA 20-541/S-006. Arimidex (anastrozole). Specifically, your submission dated 11-1-99.

COMMENTS:

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

Please provide the SAS programs that were used to produce the statistics in Tables ST1-ST199 in volume 6.18 and Tables ST1-ST205 in volume 6.33. If the programs have already been included in the application, please direct us to its location within the NDA.

Thank you,

/S/

Amy Chapman

CC: Orig. NDA 20-541/sc
HFD-150/Div. File
HFD-150/Chapman

DP

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Chapman, CSO
Fax: 302-886-2822	**Fax:** (301) 827-4590
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 1-4-00

Re: NDA 20-541/S-006. Arimidex (anastrozole). Specifically, your submission dated 11-1-99.

COMMENTS:

In regards to your new supplemental application, see the attached biopharmaceutical comments. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Chapmar

cc Orig. NDA 20-541/S-006
HFD-150/Div. File
HFD-150/C [illegible]

Biopharm

The Human Pharmacokinetics and Bioavailability section of this NDA appears to be filable from Clinical Pharmacology and Biopharmaceutics perspective. The NDA has been indexed, paginated and organized in a manner to allow substantive review to begin. However, we would like to have you provide the following information:

1. Electronic raw data for the three studies provided in Section 6 of the sNDA, such as Appendix G for studies 1033IL/0033 and 1033IL/0035 and the tables showing the raw data in the report text for study A-15-12 (preferably in Excel format).

2. Electronic raw data for the bioequivalence study report 6157IL/0002 (preferably in Excel format).

3. Raw data for in-study assay validation for the three studies provided in Section 6 of the NDA.

4. The translations from Japanese to English for parts of the report of study A-15-12 if necessary in the future.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Div File

Food and Drug Administration
Rockville MD 20857

NDA 20-541/S-006

NOV - 5 1999

Zeneca Pharmaceuticals
1800 Concord Pike, PO Box 15437
Wilmington, DE 19850-5437

Attention: Sandra Bihary, MSN
Executive Director, Regulatory Affairs

Dear Ms. Bihary:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Arimidex (anastrozole) Tablets

NDA Number: 20-541

Supplement Number: S-006

Date of Supplement: November 1, 1999

Date of Receipt: November 1, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 31, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

/S/

11-5-99

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20541/S-006
HFD-150/Div. Files
HFD-150/CSO/Amy C. Chapman

AC 11-5-99

SUPPLEMENT ACKNOWLEDGMENT

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Chapman, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
5Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 8-11-99

Re: __ Arimidex. Specifically submission dated 6-25-99, serial # Request for a pre-sNDA meeting and your facsimile of 8-10-99.

COMMENTS:

We acknowledge your facsimile of 8-10-99 in which you requested further clarification of our responses (faxed to you 8-9-99) to your questions outlined in the meeting package dated 7-23-99. See the attached for further clarification. We also agree that if there are no further requests for clarification, the industry meeting scheduled for tomorrow, 8-12-99 at 1:00pm, should be canceled. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Chapman

cc: Orig
HFD-150 /Div. File
HFD-150 /Chapman

In Studies 1033IL/0030 and 1033IL/0027, the majority of patients [302 out of 353 patients in trial 0030 (86%) and 434 out of 668 patients in trial 0027 (65%)] in both treatment groups definitely had metastatic disease (Stage IV).

However, there are patients who only had soft tissue disease [51 out of 353 patients in trial 0030 (14%) and 234 out of 668 patients in trial 0027 (35%)]. It may not be responsible to ascertain from out database whether individual patients in this group had Stage IV disease, or were Stage III. Zeneca proposes to include in the sNDA a listing of these patients.

In addition, Zeneca will review the database to determine whether it is possible to identify further the patients with soft tissue disease. Zeneca will communicate our findings to the Agency in the near future, prior to the sNDA submission. Does the Agency find this approach acceptable?

FDA Response:

1. In each trial, the numbers of patients who are not known to definitely have stage IV disease equal the numbers of patients who are known to have only soft tissue disease. Please clarify if these are, in fact, the same patients.

2. In the absence of knowing stage of disease, the following information on patients with soft tissue disease would be useful:

- Do the patients with soft tissue disease only have disease limited to the chest wall (including skin and breast)?
- If so, is the lesion in the breast?
- If so, did the patient have primary surgery on the breast—this information might be contained in the past history.
- If patient has disease limited to the chest wall and it is not in the breast, is it (chest wall) skin?
- Is there balance between the arms of the trial?

These questions may be answered in the NDA. Including a listing of those patients could be helpful. It is unknown at this time whether case report forms on these patients would be helpful, but this can be answered at the time of the review of the NDA.

As the Agency indicated that demonstration of bioequivalence is not required, but the study results are needed to interpret study 0027, Zeneca proposes to submit the Bioequivalence study results (Trial 6157/0002) within the 60 days review period after the sNDA submission. Does the Agency agree?

Yes, the Agency agrees that the Bioequivalence study results may be submitted within 60 days of review period.

FAX

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

To: Laura Garcia Davenport, Zeneca	**From:** Amy Chapman, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 5	**Date:** 8-9-99

Re: IND . Arimidex. Industry meeting scheduled for 8-12-99 at 1:00pm EST.

COMMENTS:

Attached are our DRAFT replies to your questions outlined in the meeting package dated 7-23-99 for the pre-NDA meeting scheduled for 8-12-99 at 1:00pm EST. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Chapman

CC: Orig. IND
HFD-150 / Div. File
HFD-150 / Chapman

1. **Zeneca believes that the efficacy data from the First-line Clinical Trial Program supports a sNDA for Arimidex for the first-line treatment of advanced breast cancer in post-menopausal women for the following reasons:**

   -The efficacy data generated from the core trial 1033IL/0027 meet the criteria for equivalence for the two primary endpoints of time to progression and objective-response rate.

   -The efficacy data generated from the core trial 1033IL/0030 meet the criteria for equivalence for the two primary endpoints of time to progression and objective-response rate.

   -In each core trial, the results from the protocoled primary analysis (adjusted) were supported by the results from the secondary analysis (unadjusted). Similarly, the results from the intent to treat population analysis (ITT) and per-protocol (PP) analysis were consistent.

   Does the Agency agree?

FDA Response:

- We agree that the data support submission of an sNDA.

2. **Zeneca believes that the favorable risk/benefit profile of Arimidex supports the filing of a sNDA for the claim: Arimidex is indicated for the first-line treatment of post-menopausal women with advanced breast cancer.**

Does the Agency agree?

- We agree that the data support submission of an sNDA. In addition, and as mentioned in our meeting minutes of May 20, 1999 (faxed to you 6-4-99), "It has come to our attention over the past several years that the term "advanced" may have different meanings. Please be prepared to clarify in the NDA if the patient population has metastatic or stage IV disease." Specifically, if patients with stage 3 disease are to be included, these patients must be identified for review.

3. **Trial 1033IL/0030 and Trial 1033IL/0027 used different tamoxifen formulations. As Trial 1033IL/0030, which used the US formulation, meet the criteria for equivalence for both primary endpoints, Zeneca believes that the Nolvadex bioequivalence study (Trial 6157/0002) is no longer needed and therefore, it will not be submitted with the sNDA, but will be submitted when data are available.**

Is this acceptable to the Agency?

- No. Demonstration of bioequivalence is not required, but the study results are needed to interpret study 27 and should be submitted with the sNDA.

Additional Comments:

- Pooled analysis is not likely to be permitted in the labeling due to the differences in the study results and formulations.

ASTRAZENECA PHARMACEUTICALS

Regulatory Affairs Department

Wilmington, DE 19850

RAPIFAX RAPIFAX RAPIFAX

Date: 8/31/00

Pages to follow this lead sheet: 1

Rapifax message for: Amy Baird

Rapifax message from: Louisa Garcia-Davenport M.S.

Please make copies for:

Please confirm rapifax to 1-302-886-2822- Thank You

AstraZeneca

SENT VIA RAPIFAX AND UNITED PARCEL SERVICE

AUG 3 1 2000

Dr. Richard Pazdur
Division Director
Division of Oncology 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: ARIMIDEX® (anastrozole)
NDA 20-541/S-006
Response to FDA Request for Information

Reference is made to FDA correspondence of August 31, 2000, in which the Agency provided clinical comment.

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

1. **Please commit to the following Phase 4 commitment. Do not hesitate to call should you have any questions.**

   To submit annual safety and survival updates for studies 0027 and 0030 until 75% of the patients are deceased.

   AstraZeneca agree to the above Phase 4 commitment.

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

Sincerely,

Laura E. García-Davenport, M.S.
Senior Product Manager
Regulatory Affairs Department
(302) 886-7533
(302) 886-2822 (fax)

LGD/jr

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19850-8355