CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-541/S-010

Administrative Documents

AstraZeneca Pharmaceuticals LP
ZD1033 (anastrozole, ARIMIDEX®)

PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

For further information regarding this section, please contact:

Margaret G. Melville, MS
Regulatory Affairs Director
(302) 886-2118
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

ARIMIDEX® (anastrazole) Tablets
NDA 20-541

Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

Certification

Pursuant to 21 CFR Section 314.53(d)(ii), the Applicant certifies that US Patent No. Re 36,617, information relative to which has been submitted previously, covers the formulation, composition and/or method of use of ARIMIDEX® (anastrazole) Tablets which is the subject of this supplemental new drug application.

George A. Gilbert

EXCLUSIVITY SUMMARY for NDA # 20-541 SUPPL # SE1-010

Trade Name ARIMIDEX Generic Name anastrozole

Applicant Name AstraZeneca Pharmaceuticals HFD- 150

Approval Date 9-5-02

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X /

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-541 ARIMIDEX

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # **ATAC Trial 1033IL/0029**

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 **ATAC** YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 **ATAC** YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #**1033IL**, Study # **0029**

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 **ATAC**

IND # [redacted] YES /_X_/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Richard Pazdur
9/5/02 06:16:09 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-541 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 010

Stamp Date: 3-5-02 **Action Date:** 9-5-02 **HFD-**150

Trade and generic names/dosage form: ARIMIDEX (anastrozole) Tablets

Applicant: AstraZeneca Pharmaceuticals **Therapeutic Class:** 5010200

Indication(s) previously approved: ARIMIDEX is indicated for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

ARIMIDEX is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy rarely responded to ARIMIDEX.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: ARIMIDEX is indicated for adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Is there a full waiver for this indication (check one)?

✔ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
✔ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

AstraZeneca Pharmaceuticals LP
ZD1033 (anastrozole, ARIMIDEX®)

DEBARMENT CERTIFICATION

For further information regarding this section, please contact:

Margaret G. Melville, MS
Regulatory Affairs Director
(302) 886-2118
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

ITEM 16 - CERTIFICATION STATEMENT

Re: Arimidex NDA 20-541/S-010

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP, that we did not use and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b)

Sincerely,

Executive Director, US Regulatory Affairs

TELEPHONE CONFERENCE MEETING MINUTES

MEETING DATE: December 18, 2001 **TIME:** 4:00pm **LOCATION:** B

IND/NDA IND [redacted]

Meeting Request Submission Date: 11-26-01
Briefing Document Submission Date: 12-3-01
Additional Submission Dates: 12-13-01

DRUG: Arimidex (anastrozole) Tablets

SPONSOR/APPLICANT: AstraZeneca Pharmaceuticals

TYPE OF MEETING:

1. Pre-NDA with a discussion regarding the results from the Arimidex adjuvant breast cancer program.

FDA PARTICIPANTS:

Richard Pazdur, M.D., Division Director, DODP
Alison Martin, M.D., Clinical Team Leader, DODP
Patricia Cortazar, M.D., Clinical Reviewer, DODP
John Leighton, Ph.D., Supv. Pharmacologist, DODP (pre-only)
Gang Chen, Ph.D., Statistical Team Leader, DODP
Peiling Yang, Ph.D., Statistical Reviewer, DODP
Rajeshwari Sridhara, Ph.D., Statistical Reviewer, DODP
John Duan, Ph.D., Biopharmaceutical Reviewer, DODP
Lilia Talarico, M.D., Acting Assoc. Director, DODP
Amy Baird, Consumer Safety Officer, HFD-150

INDUSTRY PARTICIPANTS:

Richard Hellmund, Global Project Statistician
Mark Steinberg, M.D., Global Med. Dir., Clinical and Med. Affairs
Margaret Melville, M.S., US Regulatory Affairs Director
Dai Davies, Ph.D., Toxicology Proj. Leader, Global Safety Assessment
David Bialek, Pharm.D., Regulatory Project Manager
Shamim Ruff, Global Regulatory Director
Alison English, Global Product Director
Julie Charlesworth, Project Manager
Peter Berry, Medical Communications Scientist
Teresa Torello, Sr. Reg. Publishing Assoc.; Oncology TA Submission Leader
Linda Faux, Sr. Global Project Manager
Tarek Sahmoud, M.D., Director of Clinical Research
Mark S. Scott, Ph.D., Executive Director, Regulatory Affairs
Gerard Kennealey, Vice President, Drug Development
Shawn P. O'Brien, Oncology Group Director
Brian Stevenson, Arimidex Product Manager

MEETING OBJECTIVES:

1. Discuss sponsor's questions in briefing document dated 12-3-01.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **AstraZeneca believes that the Arimidex ATAC data represent a significant advance in the hormonal treatment of early post-menopausal breast cancer, and that the sNDA should be granted a Priority Review. Does the Agency agree?**

   FDA Response:

   - We agree that Arimidex sNDA could be granted a priority review. At the time of the NDA submission FDA will communicate the final decision on granting a priority review.

2. **AstraZeneca proposes an expedited and rolling submission of the Arimidex ATAC data as described above. AstraZeneca proposes to commence the submission on December 21, 2001, and that this filing data start the User Fee Goal Clock. Does the Agency agree?**

   FDA Response:

   - No, we do not agree. Please formally request a Fast Track Designation to allow a rolling submission (Guidance for Industry Fast Track Drug Development Programs-Designation, Development and Application Review). However, regardless of whether you are granted Fast Track Designation, the User Fee Goal Clock will not start until the final piece of the sNDA is submitted. We will attempt to review this application as quickly as possible before a six month due date. However, review issues may emerge which prohibit a prospective formal commitment to this. This application will be considered a complex application that with more than 9,000 patients and subprotocols may require the allocation of considerable resources.

3. **AstraZeneca has proposed an updated Table of Contents to Item 5. AstraZeneca will provide these Study Reports in electronic format with bookmarks, as previously agreed, and will not include hypertext linking. Does the Agency agree with the amended content and format of Item 5?**

   FDA Response:

   - Yes.

4. **As the Arimidex ATAC Trial is the sole support for this sNDA, AstraZeneca requests the Agency waive the requirements of an HPB, ISE, ISS. All required information will be contained in the Main ATAC CSR. Does the Agency agree?**

FDA Response:

- Please submit a table of other trials of Arimidex in the adjuvant setting and other trials (e.g., Phase 1 of the combination) besides ATAC that will be submitted in this sNDA. This will assist us in answering this question.

  Discussion: ATAC trial will be submitted as the sole support for proposed indication. No other adjuvant trials or phase 1/2 exploratory trials will be submitted.

- Results of the combination arm should be explained. Therefore, an HPB should be submitted for our review.

- Are there animal data that address the inferior efficacy of the combination vs. single agent Arimidex?

  Discussion: Sponsor to submit literature data regarding what studies have been conducted in animal with the combination drug product.

5. **AstraZeneca proposes a rolling submission for Item 12, CRFs. Does the Agency agree with the proposed rolling submission schedule?**

FDA Response:

- See answer to question 2.

6. **AstraZeneca requests the Agency waive the requirement for a 4MSU. Does the Agency agree?**

FDA Response:

- No, the 4-month safety updated should be submitted. The median follow-up for this adjuvant study is only slightly over two years. The safety database could be improved with a 4-month safety update. To make such a submission meaningful, the cutoff data should be timed 4 months after the NDA clock starts.

7. **AstraZeneca and FDA have discussed the need for ODAC review of the ATAC data. Can the Agency comment on when the Arimidex sNDA could be reviewed by ODAC?**

FDA Response:

- No, it is premature to answer this question.

The meeting was concluded at 5:00pm.

/S/

Amy Baird
Consumer Safety Officer
Minutes Preparer

Concurrence Chair: /S/

Patricia Cortazar, M.D.
Clinical Reviewer

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

/s/

Amy Baird
6/26/02 02:12:33 PM

Patricia Cortazar
7/3/02 11:48:15 AM

TELEPHONE CONFERENCE MEETING MINUTES

MEETING DATE: October 15, 2001 **TIME:** 2:00pm **LOCATION:** B

IND/NDA IND [redacted]

Meeting Request Submission Date: 9-10-01
Briefing Document Submission Date: 9-10-01
Additional Submission Dates: 10-4-01

DRUG: ARIMIDEX (anastrozole) Tablets

SPONSOR/APPLICANT: AstraZeneca Pharmaceuticals

TYPE OF MEETING:

1. Pre-sNDA.

2. **Proposed Indication:**

FDA PARTICIPANTS:

Richard Pazdur, M.D., Division Director, DODP
Alison Martin, M.D., Clinical Team Leader, DODP
Patricia Cortazar, M.D., Clinical Reviewer, DODP
Susan Honig, M.D., Clinical Reviewer, DODP
Margaret Brower, Ph.D., Pharmacology Reviewer, DODP
Gang Chen, Ph.D., Statistical Team Leader, DODP
Rajeshwari Sridhara, Ph.D., Statistical Reviewer, DODP
Atiqur Rahman, Ph.D., Biopharmaceutical Team Leader, DODP
John Duan, Ph.D., Biopharmaceutical Reviewer, DODP
Amy Baird, Project Manager, DODP

INDUSTRY PARTICIPANTS:

David Bialek, PharmD., Regulatory Project Associate
Bruce Birmingham, Ph.D., Sr. Clinical Scientist, Experimental Medicines Group
Dai Davies-Toxicology Project Leader, Global Safety Assessment
Laura Garcia-Davenport, M.S., Assoc. Dir., Regulatory Affairs
Stephen L. Harrison-Clinical Program Analyst, Global Clinical Development
Richard Hellmund-Global Project Statistician
Stephen P. Rubin, M.D., Assoc. Director, Clinical Research
Mark S. Scott, Ph.D., Exec. Dir., Oncology Regulatory Affairs
Mark Steinberg, M.D., Medical Dir., Clinical and Medical Affairs
Teresa Torello, Sr. Regulatory Submission Publishing Associate

MEETING OBJECTIVES:

1. Discuss sponsor's questions in briefing document dated 9-10-01 (serial # 455).

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Chemistry, Manufacturing and Controls

1. **Drug substance information within the Chemistry, Manufacturing, and Controls (CMC) section of the NDA for BRAND X will reference the CMC data filed in the ARIMIDEX NDA 20-541 and the NOLVADEX NDA 17-970. Drug product information will be provided as outlined in section 5.1 of this document.**

   In the ARIMIDEX sNDA all Chemistry, Manufacturing and Controls (CMC) information relating to ARIMIDEX drug substance and drug product and to NOLVADEX drug substance and drug product will be provided by cross-reference to NDA 20-541 and NDA 17-970 as described in section 6.1 of this document.

   Does the Agency accept AstraZeneca's proposals for the CMC section of the BRAND X NDA and ARIMIDEX sNDA?

   FDA Response:

   - Yes. Please include the following information in the NDAs to be submitted:

   - The name and address of all facilities involved in the manufacture of the drug substance and the drug product, and the contact persons and telephone numbers.
   - The specific location of cross-referenced information (e.g., document type, submission dates and pages).

Non-Clinical Pharmacology and Toxicology

2. **AstraZeneca intends to resubmit the ARIMIDEX oncogenicity study reports, as well as other relevant pre-clinical reports that support the adjuvant use of BRAND X in the NDA. The study reports to be included in the NDA are described in section 5.2 of this document. All other Non-clinical Pharmacology and Toxicology reports will be provided by cross-reference to data on file within the Non-clinical Pharmacology and Toxicology Sections of ARIMIDEX NDA 20-541 and NOLVADEX 17-970.**

   In the ARIMIDEX sNDA the Non-clinical Pharmacology and Toxicology reports to be provided are described in section 6.2 of this document. As all other reports have been previously submitted to NDA 20-541, they will be included by cross-reference.

Does the Agency accept AstraZeneca's proposals for the Non-clinical Pharmacology and Toxicology sections of the BRAND X NDA and the ARIMIDEX sNDA?

FDA Response:

- Yes. Resubmittal and cross-reference of relevant preclinical studies that support the NDA for Brand X as well as the sNDA supporting the use of Arimidex alone or in combination with Nolvadex for adjuvant treatment of breast cancer in postmenopausal women is acceptable.

- Studies which have not previously been submitted for the NDA should include complete data as well as line listings (e.g., study TKR/2963).

Human Pharmacokinetics and Bioavailability

3. **The Human Pharmacokinetics and Bioavailability (HPB) section for the BRAND X NDA will include the reports described in section 5.3 of this document. All other HPB information supporting the BRAND X NDA will be included by cross-reference to ARIMIDEX NDA 20-541 and NOLVADEX NDA 17-970.**

   The Human Pharmacokinetics and Bioavailability (HPB) for the ARIMIDEX sNDA will be cross-referenced in its entirety to NDA 20-541 as described in section 6.3 of this document.

   Does the Agency find AstraZeneca's proposal for the HPB acceptable?

   FDA Response:

   - Yes.

Integrated Summary of Efficacy (ISE)

4. **The ISE for the Brand X NDA will focus on the results from the ARIMIDEX/NOLVADEX combination arm of trial 1033IL/0029. If superior efficacy is identified in both the combination (ARIMIDEX/NOLAVDEX) arm and the ARIMIDEX monotherapy arm, a prospective exploratory analysis will be presented as described in section 5.4 of this document.**

   The ISE for the ARIMIDEX sNDA will focus on the results from the ARIMIDEX monotherapy arm as well as the ARIIMIDEX/NOLVADEX combination arm of study 1033IL/0029. If equivalence of the ARIMIDEX monotherapy arm with NOLVADEX is identified, AstraZeneca will relate these results to the evidence from the EBCTCG Overview (Lancet 1998) to

assess the amount of NOLVADEX effect that is preserved by ARIMIDEX. This is described further in section 6.4 of this document.

Does the Agency agree?

FDA Response:

- A cut-off criterion of 1.25 ensures preservation of only 59% effect of Nolvadex by Arimidex . Given that the study population under consideration has a survival advantage, this may not be an acceptable non-inferiority margin. The proposed criteria of a hazard ratio of 1.25 for a non-inferiority claim will be a review issue.

- As you have pointed out, the estimate of the control effect from the review article includes patients pre- and post-menopausal, all ER/PR status (+, -, or unknown), and differing durations of treatment with tamoxifen. An effort should be made to find a better estimate of the control effect by including studies with post-menopausal patients only and those studies in which 5 years of tamoxifen was administered.

- It is possible that the ATAC population will be different from the 'Overview' population in all or some of these characteristics. This needs to be addressed in the non-inferiority analysis.

- We believe that it is important to conduct a per protocol analysis with ER/PR + patients only, since ER – patients do not respond to tamoxifen.

Integrated Summary of Safety (ISS)

5. **The ISS for the BRAND X NDA will focus on the safety data generated from the combination use of ARIMIDEX and NOLVADEX in the ATAC trial as described in section 5.5 of this document.**

   The ISS for the ARIMIDEX sNDA will describe the safety data generated from the use of ARIMIDEX alone and in combination with NOLVADEX as described in section 6.5 of this document.

   Does the Agency agree?

   FDA Response:

   - Yes.

   - Please report the total number of fractures and number of fractures by subcategory (spine, hip, wrist).

Proposed Format of Electronic Submission

6. **The proposed format of the electronic submission for the Brand X NDA is described in section 5.6 of this document.**

   The proposed format of the electronic submission for the ARIMIDEX sNDA is described in section 6.6 of this document.

   Does the Agency agree with the format of the electronic submissions?

   FDA Response:

   - The proposed submission of electronic data is adequate. It will be helpful if we have the opportunity to review and comment on a sample of the datasets before the NDA submission. Submission of all primary datasets in a usable format is a critical element of the electronic submission.

Statistical Methods for Multiple Comparisons

7. **Since the analysis of ATAC will include two treatment group comparisons with NOLVADEX (ARIMIDEX versus NOLVADEX, and combination versus NOLVADEX), there is a need to control the overall type 1 error rate, otherwise known as the false-positive error rate. The statistical analysis plan for ATAC specifies that the type 1 error rate will be controlled by using the Hochberg method (Hochberg 1988), to simultaneously compare ARIMIDEX with NOLVADEX for non-inferiority and compare combination with NOLVADEX for superiority. Once these comparisons have been performed, ARIMIDEX and NOLVADEX will be compared for superiority, provided ARIMIDEX has been shown to be non-inferior to NOLVADEX.**

   No adjustment for multiple comparisons was specified in the ATAC protocol. In response to Agency comments received on October 10, 2000 the Hochberg method has been prospectively included in the ATAC statistical analysis plan, which has been provided to the Agency prior to data base lock (scheduled for October 2001). This methodology to adjust for multiple comparisons has been identified as suitable for the ATAC trial after consultation with two external experts in this field, ———

Does the Agency agree that Hochberg is a suitable method to adjust for the multiple comparisons in the ATAC trial?

FDA Response:

- The adjustment of the nominal significance you have proposed is acceptable.

- Multiple comparisons using Hochberg's sequentially rejective procedure is acceptable. However, we recommend comparing Arimidex versus Arimidex + Nolvadex treatment arms to be included in the first step of simultaneous comparisons and subsequent steps to be modified accordingly.

Percentage of random ISS narratives, case report forms and case report tabulations for all deaths and for withdrawals due to adverse events, that would be required in the NDA and sNDA.

8. **AstraZeneca anticipates that at the time of data base lock, there would be approximately 602 patients who died with and without breast cancer and approximately 975 patients who withdrew due to adverse events regardless of drug relationship.**

   What percentage of the total numbers of anticipated narratives, case report forms, and case report tabulations would the Agency like to review?

   FDA Response:

   - Please submit narratives, CRF and CRT from all deaths and adverse events for our review. You can exclude narratives and case report forms from hot flashes and vaginal discharge.

Timings of Filings and Agency Review

9. **AstraZeneca believes that the chemistry, preclinical and clinical package described in this briefing document is sufficient to support the filing of an NDA for BRAND X, ——— This NDA will be filed only if the ARIMIDEX/NOLVADEX combination arm shows superior efficacy to**

tamoxifen alone for the adjuvant treatment of breast cancer in postmenopausal women. As discussed in a teleconference with the Agency on September 27, 2000, AstraZeneca believes that as the BRAND X NDA submission will be based on superior efficacy it will receive a priority (6-month) review.

Does the Agency agree?

FDA Response:

- The timeline for the review will be determined once the NDA has been filed.
- 

10. **An sNDA for ARIMIDEX would be submitted within one month after the filing of the BRAND X NDA. This sNDA will be based on the expectation of obtaining positive results from the ATAC trial supporting the use of ARIMIDEX alone and/or in combination with tamoxifen. In the event that the ARIMIDEX single arm shows superior efficacy and potentially better safety profile than tamoxifen, AstraZeneca believes that the ARIMIDEX sNDA will also merit a priority (6-month) review.**

Does the Agency Agree?

FDA Response:

- Priority review status could be granted if Arimidex shows convincing superior efficacy to tamoxifen and/or the combination shows superiority to Arimidex alone and tamoxifen alone.

The meeting was concluded at 3:00pm.

/S/

Amy Baird
Project Manager
Minutes Preparer

Concurrence Chair: /S/

Patricia Cortazar, M.D.
Clinical Reviewer

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/s/

Patricia Cortazar
4/29/02 02:42:15 PM

INDUSTRY TELEPHONE CONFERENCE MINUTES

MEETING DATE: September 27, 2000 **TIME:** 9:45am **LOCATION:** G

IND/NDA INDs [redacted]

Meeting Request Submission Date: 6-30-00
Briefing Document Submission Date: 6-30-00
Additional Submission Dates:

DRUG: IND [redacted]
IND

SPONSOR/APPLICANT: AstraZeneca Pharmaceuticals

TYPE OF MEETING:

- Discuss combination tablet of 1 mg Arimidex and 20 mg Nolvadex for the adjuvant treatment of postmenopausal women with early breast cancer.

Proposed Indication: Adjuvant treatment of postmenopausal women with early breast cancer.

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, HFD-150
John Johnson, M.D., Clinical Team Leader, HFD-150
Grant Williams, M.D., Clinical Team Leader, HFD-150
Susan Honig, M.D., Clinical Reviewer, HFD-150
Wole Odujinrin, M.D., Clinical Reviewer, HFD-150
Patricia Cortazar, M.D., Clinical Reviewer, HFD-150
Sung Kwang Kim, Ph.D., Chemistry Reviewer, DNDC1
Yung-Ao Hsieh, Ph.D., Chemistry Reviewer, DNDC1
Margaret Brower, Ph.D., Pharmacology Reviewer, HFD-150
Gang Chen, Ph.D., Statistical Team Leader, HFD-150
Raji Sridhara, Ph.D., Statistical Reviewer, HFD-150
Atiqur Rahman, Ph.D., Biopharmaceutical Team Leader, HFD-150
John Duan, Ph.D., Biopharmaceutical Reviewer, HFD-150
Brian Booth, Ph.D., Biopharmaceutical Reviewer, HFD-150
Amy Baird, Consumer Safety Officer, HFD-150

INDUSTRY PARTICIPANTS:

Sandra Bihary, MSN-Exec. Dir., Regulatory Affairs
Bruce Birmingham, Ph.D., Sr. Clin. Scientist, Experimental Med Group
Phil Brittain-Assoc. Dir., Project Mgmt.
Laura Garcia-Davenport, MS-Sr. Regulatory Proj. Mgr.
Margaret Melville-Global Regulatory Affairs Dir.
Gary Nunn-Toxicology Proj. Leader, Global Safety Assessment
Stephen Rubin, M.D.-Assoc. Dir., Clinical Research
Mark Steinberg, M.D., -Medical Dir., Clinical and Med. Affairs
Robert Timko, Ph.D.-Tech. Regulatory Affairs Manager
Alan Webster-Global Project Statistician

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated 6-30-00.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **The CMC package supporting the new drug product will include details of formulation, biobatch, manufacturing controls, test methods and specifications, and stability data per ICH guidelines as described in Section 3. Does the Agency find the package acceptable?**

FDA Response:

- The proposed CMC package is acceptable. The bracketed stability study design is currently under review with the statistical team. Comments will follow.

2. **The pre-clinical work filed to the ARIMIDEX NDA 20-541 and the NOLVADEX NDA 17-970 adequately support the proposed NDA, therefore no new pre-clinical studies will be conducted. The pre-clinical data will be provided by cross-reference to the Arimidex and Nolvadex NDAs. Does the Agency agree?**

FDA Response:

- No. We prefer that AstraZeneca resubmit the appropriate pre-clinical data with the application that will support the adjuvant indication. When the application [redacted] is submitted, pre-clinical data may be cross-referenced to the adjuvant supplement.

3. **AstraZeneca will conduct a bioequivalence trial in postmenopausal women with advanced breast cancer to demonstrate bioequivalence between the currently marketed ARIMIDEX 1 mg tablet and NOLVADEX 20 mg tablet [redacted] The proposal for the bioequivalence trial is described in Section 5. Does the Agency accept this proposal?**

FDA Response:

- No. We do not accept the proposal.

  You should conduct a single dose, cross over study in healthy volunteers with appropriate sampling times and adequate washout period. The protocol for the bioequivalence study should be submitted to the Agency for review.

- Please provide adequate justification for selection of subject numbers for the study.

- It is recommended that you conduct a study to evaluate the effect of food on the tablet formulation.

4. **The clinical section of the new NDA will be included by cross-reference to the clinical section of the adjuvant sNDA for the use of ARIMIDEX or ARIMIDEX/NOLVADEX in the treatment of postmenopausal women with early breast cancer. Does the Agency agree?**

FDA Response:

- Your proposal is acceptable if the adjuvant sNDA has been approved.

- The Agency has previously communicated its concerns about the ATAC protocol design, including:

  - Inclusion of ER negative patients.
  - Potential imbalance in the number of Stage I, II, and III patients.
  - Lack of prospective stratification for important prognostic factors and your plan to perform retrospective adjustments using Cox modeling.
  - The use of prior adjuvant chemotherapy, chosen by each local investigator.

- The trial results will need to clearly demonstrate the non-inferiority of Arimidex to Nolvadex with acceptable safety in order to receive a single-agent indication for Arimidex. The presently proposed statistical analysis for non-inferiority is not acceptable under current standards. You should submit a detailed statistical analysis plan for the non-inferiority analysis. In the analysis plan, the Nolvadex effect relative to placebo should be evaluated based on historical data (meta analysis), using the upper bound of the 95% CI for the tamoxifen:placebo hazard ratio, and the non-inferiority margin should preserve a clinically appropriate percentage of Nolvadex effect.

-

5. **In principle, the NDA for — tablet, which references clinical data demonstrating that the — — arm of the ATAC Trial has superior efficacy over NOLVADEX, would be eligible for 6-month priority review. Does the Agency agree?**

FDA Response:

- Priority review status is based on the superiority of the new product to standard therapy, as well as on other criteria. It is unlikely that submission of an sNDA for a — tablet, if the — has already been approved in an earlier supplement, would warrant priority review.

The telephone conference was concluded at 10:30am.

/S/

Amy Baird
Project Manager
Minutes Preparer

Concurrence Chair: /S/

Susan Honig, M.D.
Clinical Reviewer

/S/

Concurrence Chair: _____

Patricia Cortazar, M.D.
Clinical Reviewer

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

/s/

Susan Honig
4/18/01 08:28:40 AM

Patricia Cortazar
4/19/01 11:30:20 AM

MEMORANDUM of MEETING

DF

IND [redacted] rimidex (anastrozole) Zeneca Pharmaceuticals

DATE: March 20, 1997 TIME: 11-12:30 WOC2 Conf. G

MEETING PURPOSE: End of Phase 2 Meeting (sNDA) for adjuvant therapy indication.

Proposed Indication: Arimidex, ——— is indicated as adjuvant treatment of post-menopausal women with node-negative or node-positive breast cancer. One clinical trial is proposed, Protocol 1033IL/0029 (A Randomized, Double-Blind Trial Comparing Arimidex Alone with Nolvadex Alone with Arimidex and Nolvadex in Combination, as Adjuvant Treatment in Post- Menopausal Women with Breast Cancer).

MEETING BACKGROUND: This meeting was requested December 30, 1996 (received) and scheduled for February 10, 1997. On February 10, Zeneca requested to postpone the meeting in order to have time to provide additional information to the agency for preparation for discussion of the proposed adjuvant phase 3 clinical trial program. James Krook, M.D., ODAC participated in the pre-meeting on February 6, 1997.

INTRODUCTIONS: Brief introductions and opening by Zeneca. We immediately moved to discussion which included those items previously conveyed to Zeneca in our letter dated February 25, 1997.

DISCUSSION POINTS and DECISIONS REACHED:

1. Zeneca stated they have provided all available information regarding the efficacy of the combined use of Arimidex (anastrozole) and Nolvadex (tamoxifen citrate) in ER positive and ER negative breast cancer xenograft models. They do not have availability to Dr. ——— data beyond what has been provided. They do not have the raw data nor do they have data on tamoxifen alone. At this time, they think there is an ongoing study in tamoxifen alone. The agency finds this acceptable and understands that Zeneca is not planning to do any studies on xenograft models, but would appreciate any data provided by Dr. ———

2. Zeneca reiterated their commitment (as stated in their March 17, 1997 letter) to perform an *in vitro* study to determine the potential of the combination to alter the level of tamoxifen citrate DNA adducting generated by rat liver microsomes as soon as possible but also offered an alternate proposal. Zeneca stated that due to the difficulty in conducting this type of *in vitro* study, they would rather conduct a two-week *in vivo* study in rats. Following lengthy discussion of both studies, all agreed that either type of study would be acceptable. Zeneca prefers the two-week *in vivo* study in rats. The agency suggested that adding human hepatocytes to the *in vitro* study would allow comparison to the adducting potential of the rat liver microsomes. This would aid in study interpretation by allowing for interspecies comparisons. Zeneca will contemplate the agency's recommendations for the *in vitro* study and will respond with a draft protocol as soon as possible.

3. Zeneca agreed to conduct a six-month oral study in male Wistar rats using Nolvadex, and Arimidex and Nolvadex in combination (with doses and dosing schedule comparable to that proposed for the clinical trial) assessing tamoxifen citrate pharmacokinetics, DNA adducting in liver, clinical signs, body weight, food consumption, clinical pathology, gross pathology and histopathology. The study results will be submitted in the sNDA. Zeneca will draft a protocol and submit for our comment. Dr. Andrews stated that results from the two-week study noted above could potentially modify the recommendation for this six-month study.

4. Zeneca stated they are waiting for the report to be completed on Trial 1033IL/0031 which evaluates the effect of Arimidex 1 mg on the pharmacokinetics of tamoxifen citrate in post-menopausal women with breast cancer. They will submit the report as soon as available in the summer of 1997. Dr. Rahman noted that if metabolites had been assessed in that study, questions about drug interactions would have been answered. Unfortunately the question remains unanswered. It was agreed that Zeneca will submit a draft protocol for a subprotocol to the adjuvant trial to specifically address metabolites critical to determination of drug interactions and also race and ethnic differences (sparse sampling will suffice).

5. Zeneca justified the use of single agent Arimidex as adjuvant treatment of postmenopausal women with early stage breast cancer. In particular, Zeneca provided additional information on the efficacy of Arimidex as first-line therapy of metastatic breast cancer and the agency agreed that they may proceed with using Arimidex as a single agent in this trial (1033IL/0029).

6. Zeneca justified the use of the combination of Arimidex plus Nolvadex as adjuvant treatment of post-menopausal women with early stage breast cancer. Because there is no data available regarding the use of this combination in breast cancer patients, Zeneca assured the agency that they will demonstrate diligence in monitoring all patients receiving the combination. The agency noted Zeneca's caution and therefore, the combination use is allowed.

7. Zeneca discussed the inclusion of post-menopausal women with ER-negative tumors on this trial. The agency requested that language be inserted in the informed consent stating that the chances of ER-negative females responding is less than that of ER-positive females. Zeneca agreed to provide a draft of the proposed language for our review and comment as soon as possible. The agency noted that inclusion of this ER-negative population in this study could not be a basis for labeling.

8. The inclusion of patients with prior chemotherapy on this trial was discussed. The agency would prefer that if such patients must be enrolled, the choice of the chemotherapy regimen should be specified, at least by center, rather than leaving the choice of chemotherapy up to the individual investigator. Zeneca prefers not to specify chemotherapy by center and reassured the agency that they are confident an imbalance will not occur. The agency deferred to Zeneca's preference based on their agreement to

provide extensive detailing on the chemotherapy, drugs, course length etc.

9. The agency agreed that the proposed definition of equivalence between Arimidex vs Nolvadex is acceptable.

10. The agency prefers that stratification be done prospectively at the time of randomization for baseline estrogen receptor status, nodal status, primary tumor size, previous chemotherapy, and age.

11. The agency prefers that the primary analysis should be done using the Logrank test. Exploratory analysis using the Cox model for a pre-specified set of covariates should be supported by other tests, i.e. stratified Logrank test. Concerns about baseline imbalances of prognostic factors were raised since the study is not stratified. Zeneca stated they will use the Cox model for the primary analysis and will specify the covariates carefully. In addition, Zeneca stated that the purpose of the interim look, scheduled to take place when half of the expected number of events have occurred, is to detect inferiority of the experimental treatment.

    Concerns were raised about the timing of the major analysis and whether or not there will be enough events to show equivalence, and about adjustments of any subsequent analysis performed after the major analysis, since these subsequent analyses could be considered as interim analyses. Zeneca acknowledged these concerns.

12. Zeneca will attempt to assure accrual of equal numbers of Stage I and II breast cancer patients on this trial. The agency noted that this can be achieved via unblinded monitoring of proportions of each disease stage during the course of the trial. Zeneca acknowledged that if the ratio is different from 50/50, there may be an effect on time to recurrence.

13. The agency noted that depending on the results obtained, the proposed single pivotal study in 6000 patients may support the proposed indication of Arimidex, for administration either alone or in combination with Nolvadex as adjuvant treatment of post-menopausal women with early stage breast cancer. The proposed indication for node-negative and node-positive breast cancer may be too broad (will depend on the population of patients with Stages I and II breast cancer enrolled, and the results obtained).

14. The agency added that the most recent information on ocular events must be included in the investigators brochure and the informed consent.

ACTION ITEMS:

1. Zeneca will submit a draft protocol for the two-week study for comment as soon as possible followed by the six-month *in vivo* study draft protocol.

2. Zeneca will submit a draft protocol addressing the metabolites critical to determination of drug interactions and race and ethnic differences as soon as possible.

3. Zeneca will submit draft language regarding ER-negative patient response and ocular events to be included the informed consent.

There were no unresolved issues. The meeting was concluded at 12:45 pm.

ATTENDEES:

FDA/HFD-150
Robert Justice, M.D., Deputy Division Director, Division of Oncology Drug Products
Julie Beitz, M.D., Team Leader and Reviewer
Karen Johnson, M.D., Medical Officer
Margaret Brower, Ph.D., Pharmacology
Paul Andrews, Ph.D., Pharmacology Team Leader
Tony Koutsoukos, Ph.D., Statistician
Atiqur Rahman, Ph.D., Clinical Pharmacology and Biopharmaceutics, Team Leader
John Duan, Ph.D., Clinical Pharmacology and Biopharmaceutics
John M. Strong, Laboratory of Clinical Pharmacology
Leslie Vaccari, Project Manager Note: James Krook, M.D., ODAC participated in pre-meeting

Zeneca
Sandra Aquaviva, Manager, Marketed Products Group, Drug Regulatory Affairs
Nigel C. Barass, Ph.D., International Project Toxicologist, Safety Of Medicines
Mike Dukes, Ph.D., Senior Scientist, Chemistry Metabolism & Endocrinology
Barbara Ewing, Ph.D., Assistant Director, Drug Disposition and Metabolism
David C. Lee, MBChC, International Project Physician, Medical Affairs
Margaret Melville, Senior Regulatory Specialist, Drug Regulatory Affairs
Terry Orton, Ph.D.Senior Scientist, Safety of Medicines
Mark M. Steinberg, M.D., Associate Director, Medical Affairs
John C. Topham, Ph.D, Safety Evaluation Manager, Safety of Medicines
Alan Webster, MSc, International Project Statistician, Medical Research

/S/
Leslie Vaccari, Project Manager
Minutes Preparer

Concurrence.
Final
5-29-97

/S/
Robert Justice, M.D.
Deputy Director
Division of Oncology Drug Products

cc: Original IND
HFD-150/Div File
HFD-150/DPease
HFD-150/LVaccari
HFD-150/all attendees

R/D reviewed by: JBeitz/4-4-97
MBrower/4-7-97
PAndrews/4-8-97
TKoutsoukos/4-10-97
ARahman/4-14-97
JDuan/4-9-97

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confidential

commercial

information

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-541	Efficacy Supplement Type SE1-	Supplement Number: 010	
Drug: ARIMIDEX (anastrozole) Tablets		Applicant: AstraZeneca Pharmaceuticals	
RPM: Amy Baird		HFD-150	Phone #: 594-5771
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	9-5-02
❖ Special programs (indicate all that apply)	( ) None Subpart H (X) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) (X) Fast Track (X) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	✔
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	dated 9-5-02
• Most recent applicant-proposed labeling	8-27-02
• Original applicant-proposed labeling	12-20-01
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	✔ Tamoxifen
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	9-4-02
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✔
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	3-20-97
• Pre-NDA meeting (indicate date)	10-15-01
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9-5-02; 9-5-02; 8-13-02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	9-5-02
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	9-3-02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	8-14-02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	5-15-02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	5-15-02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8-9-02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

?/02

AstraZeneca

Date:_____

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

Re: NDA 20-5041/S-010
ARIMIDEX® (anastrozole) Tablets
Response to Subpart H and Phase IV Commitments

Dear Dr. Pazdur:

Reference is made to AstraZeneca Pharmaceuticals LP (AstraZeneca) March 4, 2002 submission of the Supplemental New Drug Application (sNDA) supporting the use of Arimidex for the Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. Additional reference is made to FDA rapifax communication dated September 4, 2002, outlining the Subpart H and Phase IV commitments for the above referenced sNDA.

The purpose of this submission is to advise the Agency that AstraZeneca accepts the wording for the Subpart H and Phase IV commitments as outlined in the September 4, 2002 rapifax.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Please direct any questions or requests for additional information to me, or in my absence, to Laura E. García-Davenport, Associate Director, Project Management, at (302) 886-7533.

Sincerely,

David A. Bialek, Pharm.D.
Regulatory Project Manager
Regulatory Affairs
(302) 886-5825
(302) 886-2822 (fax)

Desk Copy: Ms. Amy Baird, HFD No. 150, Room No. 2106

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

A70809 (8/00)

AstraZeneca
US Regulatory Affairs

FAX

Date: September 5, 2002
Number of pages including cover sheet: 2
Re: Response to Subpart H and Phase IV Commitments

To:	Amy Baird	From:	David Bialek, PharmD US Regulatory Affairs
Phone:	301-594-5771	Phone:	302-886-5825
Fax phone:	301-594-0498	Fax phone:	302-886-2822
CC:			

REMARKS:

☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Amy,

Please find enclosed AstraZeneca's acceptance of the wording for the Subpart H and Phase IV commitments. This should conclude correspondence prior to receipt of FDA's approval letter.

Should you have any questions, please feel free to contact me.

Thank you in advance,
David Bialek

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To:	Dave Bialek, Pharm.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover): 2		**Date:**	September 4, 2002

Re: NDA 20-541/S-010 Arimidex. Request for Phase 4 commitments and proposal for accelerated approval.

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Attached are the Subpart H and Phase 4 requests that will be in the action letter for Arimidex. Please provide a written commitment to the Division's requests. Please call should you have any questions.

Thank you,

/S/

Amy Baird

Subpart H post marketing commitments

1. To submit a complete report of the updated ATAC data during 2004 to verify the safety and efficacy of Arimidex in the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. The report will include an analysis of efficacy in the subgroup of patients who have received chemotherapy.

2. To conduct a double-blind, randomized, comparison trial using Arimidex with and without bisphosphonate therapy in early breast cancer patients. The design of this trial will be finalized in consultation with the Agency by November 1, 2002.

3. To submit a subprotocol and conduct a study to evaluate the development of hyperlipidemia and control of hyperlipidemia in patients on the ATAC trial.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this post marketing commitment must be clearly designated "Subpart H Post Marketing Commitments."

Phase 4 commitments

1. In the NDA Annual Progress Reports provide information regarding the incidence of the pre-specified safety events and hypercholesterolemia for the treatment arms of the ATAC trial.

2. Continue to collect data in the ATAC trial on serious adverse events including fractures and those associated with hypercholesterolemia (i.e., cardiovascular and cerebrovascular adverse events) for an additional five years following discontinuation of treatment or breast cancer recurrence. Submit the safety report summarizing these data by January 1, 2011.

3. To submit a complete report of the updated ATAC data to verify the safety and efficacy of Arimidex in the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer when all patients on the ATAC trial have completed five years of treatment and two years of follow-up (approximately June 2007). The report will include an analysis of efficacy in the subgroup of patients who have received chemotherapy

MESSAGE CONFIRMATION

09/04/02 17:29

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
09/04	00'47"	8862822	CALLING	02	OK	0000

09/04/02 17:27 NO.023 D01

Fax

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

To:	Dave Bialek, Pharm.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	September 4, 2002

Re: NDA 20-541/S-010 Arimidex. Request for Phase 4 commitments and proposal for accelerated approval.

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Laura Garcia-Davenport
Fax: 302 886-2822

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 1

Date: 8-12-02

COMMENTS: We have a request from our Arimidex statisticians for the SAS program code to convert dates from "10DEC1996" to "12/10/1996" format.

Thanks

Dotti for Amy

the content of this 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.

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Laura Garcia-Davenport
Fax: 302 886-2822

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 1

Date: 8-12-02

COMMENTS: We have a request from our Arimidex statisticians for the SAS program code to convert dates from "10DEC1996" to "12/10/1996" format.

Thanks

Dotti for Amy

08/12/02 13:30 NO.035 P01

MESSAGE CONFIRMATION

08/12/02 13:31

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
08/12	00'29"	8862822	CALLING	01	OK 0000

Fax

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

To:	Dave Bialek, Pharm.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover): 1		**Date:**	August 2, 2002
Re:	NDA 20-541/S-010 Arimidex.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Per the clinical reviewer, the following pathology reports from patients with ipsilateral recurrence are still missing:

Arimidex Arm: 0047/0001, 0211/0004, 0250/0034
Tamoxifen Arm: 0003/0011, 0211/0017, 0256/0020, 0424/0013, 0498/0015
Arimidex + Tamoxifen Arm: 0100/0017, 0235/0017, 0250/0037, 0322/0014

Please call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

08/02/02 13:22
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
08/02	00'30"	8862822	CALLING	01	OK	0000

08/02/02 13:21 FDA-DODP → 913028862822 NO.036 D01

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Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Dave Bialek, Pharm.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	August 2, 2002
Re:	NDA 20-541/S-010 Arimidex.		

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5600 Fishers Lane, Rockville, MD 20857

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 30, 2002

Re: NDA 20-541/S-010 Arimidex. Regarding FDA facsimiles dated 7-23-02 (not sent until 7-24-02) and 7-25-02.

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Regarding FDA facsimile dated 7-23-02, please disregard question #1. The Division has located these CRFs. Also, question 4 should read "Patient 0438/0011" not "Patient 0436/0019". In regards to FDA facsimile dated 7-25-02, the Division has located all but 5 of the CRFs listed in that facsimile. Please provide the following missing CRFs:

0027/0059, 0027/0066, 0449/0008, 0065/0004, 0097/0026.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

07/30/02 17:36
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/30	00'30"	8862822	CALLING	01	OK	0000

07/30/02 17:35 FDA-DODP → 913028862822 NO.032 D01

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 30, 2002

Re: NDA 20-541/S-010 Arimidex. Regarding FDA facsimiles dated 7-23-02 (not sent until 7-24-02) and 7-25-02.

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 29, 2002
Re:	NDA 20-541/S-010 Arimidex.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Per the request of the clinical team, please respond to the following request for clarification.

Patient 0002/0019 CRF states that the patient died from ovarian cancer not related to breast cancer. However, the datasets showed this patient had distal recurrence. Please comment.

Call me should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

07/29/02 16:06

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/29	00'29"	8862822	CALLING	01	OK	0000

07/29/02 16:05 NO.053 P01

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Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 29, 2002
Re:	NDA 20-541/S-010 Arimidex.		

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Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover): 1		**Date:**	July 25, 2002
Re:	NDA 20-541/S-010 Arimidex.		

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• **Comments:**

Per the clinical reviewer, please provide the following missing CRFs. Please call should you have any questions.

0008/0030, 0027/0059, 0027/0066, 0043/0002, 0059/0010, 0065/0004, 0097/0026, 0211/0006, 0211/0031, 0216/0007, 0250/0012, 0263/0027, 0265/0019, 0307/0019, 0426/0127, 0433/0013, 0435/0045, 0449/0008, 0489/0008, 0492/0001

Thank you.

/S/

Amy Baird

MESSAGE CONFIRMATION

07/25/02 11:43

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/25	00'29"	8862822	CALLING	01	OK	0000

07/25/02 11:42 NO.034 D01

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages (including cover): 1	**Date:** July 25, 2002
Re: NDA 20-541/S-010 Arimidex.	

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5600 Fishers Lane, Rockville, MD 20857

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	3	**Date:**	July 23, 2002
Re:	NDA 20-541/S-010 Arimidex.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Per the clinical reviewer, please provide the responses to the following requests for information. Please call should you have any questions.

Thank you.

/S/

Amy Baird

1. Please provide the following CRFs from patients who died during treatment:

0009/0060, 0012/0002, 0018/0101, 0113/0002, 0213/0038, 0289/0013, 0290/0020, 0298/0003, 0505/0009, 0525/0013, 0003/0025, 0010/0063, 0010/0091, 0062/0007, 0071/0006, 0153/0026, 0211/0062, 0212/0002, 0212/0039, 0234/0019, 0250/0018, 0281/0024, 0283/0031, 0301/0030, 0004/0035, 0011/0005, 0040/0003, 0070/0005, 0077/0003, 0080/0048, 0116/0003, 0201/0020, 0235/0017, 0283/0028, 0304/0007, 0307/0002.

2. Regarding patient 0011/0008, please clarify the following information from the CRF. On 11/05/1999 follow-up, it states no recurrence, but at 11/05/1999 it states axillary lymph node recurrence by clinical examination only.

3. Regarding Patient 0222/0008, CRF states cause of death was breast cancer and pyloric stenosis. No confirmed recurrence before death. Please comment on the cause of death.

4. Regarding Patient 0436/0019, CRF states cause of death was breast cancer, unknown and dementia. Please comment.

The attached JMP table is a query of the patients with loco regional recurrence who had axillary sampling and radiation therapy (see RADIOT of SO1604 where field states Y). Please provide information if the axillary regions were included in the field at the time of breast irradiation.

Subset of locoreg AXSURG samp XRT

Rows	SUBJECT of DDEMOG	RECDET	AXSURG	AXDET	RADIOT of S01604	TRTSEQ of RS01613
1	0002/0030	4	Y	1	Y	002
2	0004/0035	4	Y	1	Y	003
3	0004/0039	4	Y	1	Y	003
4	0005/0037	4	Y	1	Y	002
5	0006/0001	4	Y	1	Y	003
6	0014/0116	4	Y	1	N	003
7	0018/0036	4	Y	1	Y	001
8	0019/0010	4	Y	1	Y	002
9	0019/0026	4	Y	1	N	001
10	0049/0021	4	Y	1	Y	002
11	0059/0009	4	Y	1	Y	001
12	0062/0001	4	Y	1	Y	001
13	0062/0007	4	Y	1	Y	002
14	0067/0002	4	Y	1	N	002
15	0067/0007	4	Y	1	Y	003
16	0076/0006	4	Y	1	N	003
17	0117/0002	4	Y	1	Y	001
18	0152/0037	4	Y	1	Y	001
19	0171/0031	4	Y	1	Y	002
20	0197/0003	4	Y	1	N	003
21	0201/0008	4	Y	1	N	001
22	0212/0039	4	Y	1	Y	002
23	0213/0031	4	Y	1	Y	003
24	0214/0005	4	Y	1	Y	003
25	0307/0002	4	Y	1	N	003
26	0322/0014	4	Y	1	Y	003
27	0324/0017	4	Y	1	Y	001
28	0409/0049	4	Y	1	N	001
29	0432/0014	4	Y	1	Y	002
30	0435/0027	4	Y	1	Y	002
31	0435/0038	4	Y	1	N	001
32	0436/0010	4	Y	1	Y	001
33	0441/0005	4	Y	1	Y	002
34	0441/0009	4	Y	1	Y	002
35	0446/0011	4	Y	1	Y	001
36	0449/0005	4	Y	1	N	003
37	0450/0019	4	Y	1	N	003
38	0457/0005	4	Y	1	N	002
39	0466/0002	4	Y	1	Y	001
40	0469/0026	4	Y	1	N	002
41	0474/0012	4	Y	1	N	003
42	0475/0007	4	Y	1	N	001
43	0475/0022	4	Y	1	Y	002
44	0480/0004	4	Y	1	N	003
45	0482/0002	4	Y	1	Y	002
46	0497/0009	4	Y	1	Y	002
47	0497/0029	4	Y	1	Y	002
48	0508/0006	4	Y	1	N	003
49	0510/0006	4	Y	1	Y	001
50	0510/0031	4	Y	1	Y	003
51	0525/0013	4	Y	1	Y	001
52	0526/0018	4	Y	1	Y	003

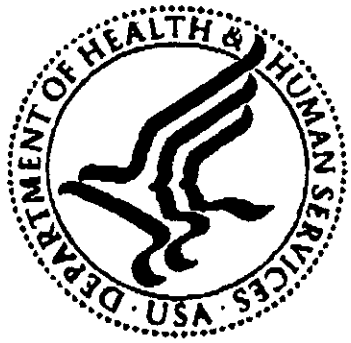
MESSAGE CONFIRMATION

07/24/02 13:48

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/24	01'11"	8862822	CALLING	03	OK	0000

07/24/02 13:46 NO.026 D01

Fax



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

To:	Dave Bialek, Pharm.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	3	**Date:**	July 23, 2002
Re:	NDA 20-541/S-010 Arimidex.		

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover): 3		**Date:**	July 17, 2002
Re:	NDA 20-541/S-010 Arimidex.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Per the clinical reviewer, please provide the following missing CRFs. Please call should you have any questions.

Thank you,

Amy Baird /S/

Table 2. Patients reporting Loco-regional Recurrence of the ipsilateral Breast as Presented in Table 36 of the CSR (Patient Population: All Randomised Patients)

Randomised Treatment	Centre	Patient
Anastrozole	0008	0013
	0008	0072
	0018	0026
	0047	0001
	0059	0009
	0117	0002
	0165	0002
	0172	0010
	0183	0004
	0185	0014
	0211	0004
	0250	0034
	0307	0008
	0307	0066
	0324	0017
	0409	0049
	0436	0010
Tamoxifen	0003	0011
	0003	0025
	0016	0007
	0019	0010
	0027	0084
	0049	0021
	0053	0011
	0067	0002
	0071	0010
	0122	0007
	0166	0007
	0168	0014
	0174	0019
	0211	0017
	0307	0024
	0424	0013
	0426	0123
	0441	0009
	0482	0002
	0486	0063
	0492	0001
	0498	0015
Anastrozole + Tamoxifen	0012	0014
	0014	0116
	0072	0018
	0076	0006
	0080	0048
	0097	0026
	0100	0017
	0167	0017

Randomised Treatment	Centre	Patient
Anastrozole + Tamoxifen	0201	0020
	0235	0017
	0250	0037
	0269	0006
	0307	0051
	0322	0014
	0449	0005
	0450	0019
	0474	0012
	0502	0010
	0526	0018

MESSAGE CONFIRMATION

07/17/02 15:05

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/17	00'48"	8862822	CALLING	03	OK	0000

07/17/02 15:03 NO.005 P01

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5600 Fishers Lane, Rockville, MD 20857

To:	Dave Bialek, Pharm.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	3	**Date:**	July 17, 2002
Re:	NDA 20-541/S-010 Arimidex.		

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5600 Fishers Lane, Rockville, MD 20857

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	1	**Date:**	July 15, 2002
Re:	NDA 20-541/S-010 Arimidex.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

- **Comments:**

Per the clinical reviewer, please perform a time to first fracture event analysis. Please call should you have any questions.

Thank you,

Amy Baird

MESSAGE CONFIRMATION

07/15/02 16:02
ID=FDA-DODP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/15	00'28"	8862822	CALLING	01	OK	0000

07/15/02 16:01 FDA-DODP → 913028862822 NO.090 P01

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Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

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Pages (including cover):	1	**Date:**	July 15, 2002
Re:	NDA 20-541/S-010 Arimidex.		

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover): 2		**Date:**	July 3, 2002

Re: NDA 20-541/S-010 Arimidex. Follow-up to telephone conversation held yesterday, 7-2-02, between yourself, Drs. Cortazar and Sridhara, and Amy Baird.

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

• **Comments:**

Per the request of the statistical and clinical reviewers, please provide the following:

1. Please submit a dataset with patient identification, treatment arm and histology from loco-regional recurrences or new primaries from the following patients:

   -From Table 17 of the Study Report, new primary contralateral breast cancer (14 + 33 + 28).
   -From Table 36 of the Study Report, ipsilateral breast cancer recurrence (21 + 31 + 20).

Regarding Table 17: Recurrence status as of data cut-off according to first confirmed event (vol 1. submitted on 3-25-02)

2. You have reported 67, 83, and 81 patients with loco-regional recurrence in treatment arms A, T, and A + T respectively. Our analysis using DDEMOG data set gives 68, 90 and 87 patients respectively for trt arms A, T and A + T. Please clarify the difference.

3. You have reported 157, 181, and 202 patients with distant recurrence in treatment arms A, T, and A + T respectively. Our analysis using DDEMOG data set gives 267, 299 and 312 patients respectively for trt arms A, T and A + T. Please clarify the difference.

Thank you,
Amy Baird

/S/

MESSAGE CONFIRMATION

07/03/02 12:25

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
07/03	00'40"	8862822	CALLING	02	OK	0000

07/03/02 12:23 NO.240 D01

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Fax:	302-886-2822	**Fax:**	(301) 594-0498
Phone:	302-886-5825	**Phone:**	(301) 594-5771
Pages (including cover):	2	**Date:**	July 3, 2002

Re: NDA 20-541/S-010 Arimidex. Follow-up to telephone conversation held yesterday, 7-2-02, between yourself, Drs. Cortazar and Sridhara, and Amy Baird.

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

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: Dave Bialek, Pharm.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-19-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide the information requested on the following pages. Please call should you have any questions.

Thank you,

/S/

Amy Baird

1. The adverse events collected in the ATAC trial show that hypercholesterolemia was more frequently reported for the Arimidex group than the Tamoxifen group. The advanced breast cancer study also demonstrated an increase in cholesterol. Tamoxifen is associated with a favorable lipid profile; although the favorable profile has not translated into a cardiovascular benefit for patients taking tamoxifen. The planned lipoprotein substudy was never completed; however if completed would have had a control group for comparison with Arimidex group. In view of the elevated cholesterol levels seen in the ATAC postmenopausal participants, please comment on the potential for cardiovascular events in women treated with Arimidex.

2. Please provide a table for the other fractures (i.e., not hip, spine or wrist/Colles) listing specific type of fracture and the numbers of patients sustaining a fracture by treatment group.

3. Provide information on the number of patients by treatment group who had more than 1 fracture event.

4. Please provide a table listing the number of patients who had a fracture by treatment group by fracture etiology (fall/traumatic, motor vehicle accident, unknown, etc.).

5. Please provide information on the number of locoregional recurrence patients who had noninvasive disease by treatment group.

MESSAGE CONFIRMATION

06/19/02 15:00

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
06/19	00'43"	8862822	CALLING	02	OK	0000

06/19/02 14:58 NO.169 001

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: Dave Bialek, Pharm.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-19-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

FAX

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-11-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide the information requested on the following pages. Please call should you have any questions.

Thank you,

/S/

Amy Baird

1. Specify the non-approved or experimental treatment received before randomization (from Table 11 page 44 or 72 of the Study Report).

2. Specify the therapy that affect sex hormone status or prevent recurrence, received prior to disease recurrence (from Table 12 page 47 or 74 of the Study Report).

3. List and specify all the non-allowed concomitant medications, date of first administration, duration of therapy, reason for therapy and repeated use of medication (such as several courses of medication for uterine bleeding).

MESSAGE CONFIRMATION

06/11/02 10:28

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
06/11	00'37"	8862822	CALLING	02	OK	0000

06/11/02 10:27 NO.121 001

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: Dave Bialek, Pharm.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-11-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

FAX

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

To: Dave Bialek, Pharm.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-7-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

The clinical reviewer who is reviewing the safety portion of your efficacy supplement has a number of questions regarding hypercholesterolemia, see the attached for requests for information. Please call should you have any questions.

Thank you,

Amy Baird

1. Please provide a table for patients with hypercholesterolemia as a new adverse event in the trial showing numbers of patients and incidence rates: Previous history of hypercholesterolemia (yes/no) by treatment.

2. How did you obtain information on hypercholesterolemia as a past medical history? Did you specifically cross check lipid lowering medications and past medical history?

3. How was the information on hypercholesterolemia as an adverse event obtained? Did you specifically check patient forms for the addition of lipid lowering medication or diet changes?

4. Please provide a table of patients reported to have hypercholesterolemia as a new adverse event by hyperlipidemia (past medical history – yes/or) by breast cancer hormone therapy.

5. Please provide a table of patients reported to have hypercholesterolemia as a new adverse event by hyperlipidemia (past history – based on lipid lower medication - yes/no) by breast cancer hormone therapy.

6. Provide a table of patients reported to have hypercholesterolemia as a new adverse event by hyperlipidemia treatment started during the trial (yes/no) by breast cancer hormone therapy.

7. Please also provide documentation concerning the death of tamoxifen patient #0406/0023. This patient is listed as having died as a result of endometrial hyperplasia; however, there is no documentation of death.

MESSAGE CONFIRMATION

06/07/02 13:06

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
06/07	00'44"	8862822	CALLING	02	OK	0000

06/07/02 13:05 NO.102 P01

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: Dave Bialek, Pharm.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-7-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

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5600 Fishers Lane, Rockville, MD 20857

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-7-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide the information requested on the following pages. Please call should you have any questions.

Thank you,

/S/

Amy Baird

1. Please provide information on history of breast biopsies, presence of AH, presence of LCIS by treatment arm.

2. Submit information on post-study therapy and crossovers.

3. Provide a listing of patients by treatment who received raloxifene during or after withdrawal from trial.

4. Provide the location of the histology of new primary contralateral breast cancer and the method of confirmation.

5. Please provide a table for patients with a musculoskeletal current illness – total number of patients and then number of patients by categories (e.g., arthritis, osteoporosis, etc.) by treatment.

MESSAGE CONFIRMATION

06/07/02 10:16

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
06/07	00'38"	8862822	CALLING	02	OK	0000

06/07/02 10:15

FAX

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

To: Dave Bialek, Pharm.D.	**From:** Amy Baird, CSO
Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-5825	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 6-7-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

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	**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:** 5-30-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide the information requested on the following pages. Please call should you have any questions.

Thank you,

/S/

Amy Baird

1. Please provide a table with the numbers of patients who developed a new contralateral breast primary after they developed a recurrence of their initial breast cancer by treatment group.

2. Provide a table showing numbers of patients and incidence rates: Biphosphonate use (yes/no) by fracture (yes/no) by treatment group. Calcium use (yes/no) by fracture (yes/no) by treatment group.

3. Provide a table for all patients who developed a fracture listing each patient with the following information: patient number, treatment received, length of study treatment (exposure) when patient developed fracture and type of fracture.

4. Provide a table showing for all patients who experienced a serious adverse event after trial treatment withdrawal: patient number, treatment received, length of study treatment, time from drug discontinuation date to serious adverse event, and serious adverse event.

5. Please provide the following CRFs:

   0030/0031, 0030/0071, 0049/0065, 0057/0063, 0093/0015, 0099/0014, 0046/0009, 0306/0008, 0449/0013, 0467/0008, 0479/0009, o496/0002, 0516/0013, 0003/0025, 0014/0017, 0019/0010, 0021/0011, 0029/0034, 0032/0019, 0113/0004, 0116/0011, 0305/0011, 0436/0085, 0486/0081, 0489/0055, 0494/0005, 0003/0058, 0005/0017, 0030/0095, 0049/0059, 0059/0001, 0093/0033, 0117/0001, 0132/0104, 0323/0046, 0416/0024, 0435/0029, 0436/0073, 0438/0024, 0450/0001, 0488/0003

6. Please provide the following:

   a. Reason why patient 0049/0070 in the Arimidex arm started tamoxifen at Visit #7 and provide the duration of the tamoxifen treatment.

   b. Reason why patient 0053/0045 in the Arimidex arm started tamoxifen at Visit #3 and provide the duration of the tamoxifen treatment.

   c. Patient 0072/0016 randomized to tamoxifen showed on visit 3.5 as receiving tamoxifen and anastrozole. Is this in addition to the trial therapy? How long did the patient receive combination treatment?

   d. Why was patient 0216/0004 receiving chemotherapy while on trial?

   e. Patient 0489/0041 randomized to tamoxifen arm received combined hormonal treatment. Please explain the reason and for how long the patient took the combined medication.

   f. Identify the non-allowed therapy that the following patients received before recurrence:

0316/0003	0029/0035	0031/0057	0408/0013	0413/0016
0025/0018	0069/0002	0219/0002	0433/0035	

MESSAGE CONFIRMATION

05/30/02 14:33

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
05/30	00'51"	8862822	CALLING	02	OK	0000

05/30/02 14:32 NO.050 P01

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	**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:** 5-30-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

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To: Laura Garcia-Davenport	**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:** 5-24-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide the information requested on the following pages. Please call should you have any questions.

Thank you,

/S/

Amy Baird

1. Please complete the following tables:

Country	Study Sites (n)	Patients Enrolled (n)
United States		
Canada		
Australia		
France		
Great Britain	122	
Belgium	5	192
Netherlands	5	7
Total		

Length of Follow-up (months)	Patients	Percentage
<12		
12-<18		
18-<24		
24-<30		
≥30		

*please send by treatment arm.

2. Information on the length of follow-up was not included in the submission. Only the median follow-up information was provided. Please provide information regarding the length of follow-up.

3. Provide the location of the table where the withdrawals as a result of death were derived. It seems that T10 5.3 and 5.4 has more deaths reported during treatment.

4. How many patients were withdrawn from the study due to fractures? If there were any, Tables 60 and 58 should be consistent.

5. Please submit information on non-allowed medications use during the trial, including date of first administration, starting date from randomization, duration of therapy, reason for therapy and data on repeated use.

MESSAGE CONFIRMATION

05/24/02 10:13

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
05/24	00'44"	8862822	CALLING	02	OK	0000

05/24/02 10:11 NO.016 P01

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	**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:** 5-24-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

FAX

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5600 Fishers Lane, Rockville, MD 20857

To: Laura Garcia-Davenport	**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:** 5-24-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide the following information. Please call should you have any questions.

Please individualize code break reasons for adverse events and investigator recommendations/other from the latest submission. We would also like to know if the patients who were unblinded for adverse events were withdrawn from the study. If so, provide code break date and study withdrawal date.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

05/24/02 10:49

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
05/24	00'29"	8862822	CALLING	01	OK	0000

05/24/02 10:47 NO.018 001

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	**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:** 5-24-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

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5600 Fishers Lane, Rockville, MD 20857

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 5-1-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

COMMENTS:

Per the clinical reviewer, please provide information regarding how many patients had their treatment code broken and reasons for breaking the code. Please call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

05/01/02 09:45

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
05/01	00'28"	8862822	CALLING	01	OK	0000

05/01/02 09:44 NO.002 P01

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	**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:** 5-1-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets.

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Fax: 302-886-2822	**Fax:** (301) 594-0498
Phone: 302-886-7533	**Phone:** (301) 594-5771
Pages, including cover sheet: 1	**Date:** 3-12-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets. Submission dated 3-4-02.

COMMENTS:

Per the chemistry reviewer:

All applications (e.g., sNDAs) requesting agency action require the submission of an EA or a claim of categorical exclusion. Under the revised 21 CFR Part 10, your supplemental new drug application qualifies for a categorical exclusion, if action on this submission does not increase the use of active moiety, or results in increased use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb.

We recommend that you review your data and determine whether an EA or a claim of categorical exclusion should be submitted. Please note that the standard expected introduction concentration (EIC) is included in the EA Industry Guidance and the calculation should be based on the kg of the active moiety used in the entire product line for Arimidex.

Please call should you have any questions.

Thank you,

/S/

Amy Baird

MESSAGE CONFIRMATION

03/12/02 12:13

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
03/12	00'33"	8862822	CALLING	01	OK	0000

03/12/02 12:12 NO.011 P01

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	**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:** 3-12-02

Re: NDA 20-541/S-010 Arimidex (anastrozole) Tablets. Submission dated 3-4-02.