CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20753

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date 04/28/99

L.C.P 4/28/99

From Lana Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products, HFD-580

Subject response to consult on Aromasin (exemestane) Tablets

To Patrick Guinn, Project Manager, Division of Oncologic Drug Products, HFD-150

Through Lisa Rarick, M.D., Director, Division of Reproductive and Urologic Drug Products (HFD-580) /S/ 4/28/99

This memorandum is in response to your consult dated February 18, 1999, received February 24, 1999 requesting input on the label for Aromasin (exemestane) Tablets. Specifically, your requested that we provide comments on two subsections: **Mechanism of Action** and **Pharmacodynamics**.

The first paragraph of the **Mechanism of Action** subsection should be revised to read:

> "Estrogens play an important role in the growth of hormone-dependent breast cancer. In premenopausal women, the principal sources of estrogen (primarily estradiol) are the granulosa cells of the developing ovarian follicle and the corpus luteum. In postmenopausal women, the principal source of circulating estradiol is the peripheral aromatase conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrone, with further conversion of estrone to estradiol. Aromatization of androgens to estrogens occurs mainly in adipose tissue but also in almost every other tissue including liver, muscle, hair follicles, and breast tissue. Treatment of advanced breast cancer has included efforts to decrease estrogen levels by ovariectomy premenopausally and by the use of antiestrogens and progestational agents both pre-and postmenopausally. In some women these interventions lead to decreased tumor mass or delayed progression of tumor growth. The inhibition of estrogen production by aromatase inhibitors is an effective and selective treatment for estrogen receptor-positive breast cancer in postmenopausal women."

The **Pharmacodynamics** subsection is acceptable as written.

cc: HFD-580/Controlled Correspondence (DRUDP-11) + incoming
HFD-580/AParekh, TvanderVlugt, SSlaughter, LRarick

Memorandum

TO: Lana Pauls

THROUGH: Shelley Slaughter, MD /S/

FROM: Theresa van der Vlugt, MD /S/

SUBJECT: Controlled Correspondence DRUDP-11, HFD-150 Request for Consultation

Date: April 15, 1999

The Request for Consultation received from HFD-150 on 2/18/99, with a due date of 4/30/99, requests a review of the proposed label for NDA 20-753, Exemestane Tablets. In particular, HFD-150 requests DRUDP review and comment on the following two sections of the proposed label, Mechanism of Action and Pharmacodynamics, wherein the effects of examestane on estrogens, the adrenal axis and receptors are claimed.

Mechanism of Action

The information provided is concise and accurate. Depending on the level of detail information to be included, I would offer the following suggestions for consideration (based on a review of the labels of approved similar aromatase inhibitors):

1) Delete—

Add---Estrogens play an important role in the growth of hormone-dependent breast cancer.

2) Delete—

3) Delete—

Add---In premenopausal women, the principal sources of estrogen (primarily estradiol) are the granulosa cells of the developing ovarian follicle and the corpus luteum. In postmenopausal women, the principal source of circulating estradiol is the peripheral aromatase conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrone, with further conversion of estrone to estradiol.

4) Delete—

Add---Aromatization of androgens to estrogens occurs mainly in adipose tissue but also in almost every other tissue including liver, muscle, hair follicles, and breast tissue.

5) Delete—

Add---Treatment of advanced breast cancer has included efforts to decrease estrogens levels by ovariectomy premenopausally and by the use of antiestrogens and progestational agents both pre- and postmenopausally (excerpted from the Arimidex® label). In some women these interventions lead to decreased tumor mass or delayed progression of tumor growth. The inhibition of estrogen

production by aromatase inhibitors is an effective and selective treatment for estrogen receptor-positive breast cancer in postmenopausal women.

No changes are proposed in the ~~second paragraph under Mechanism of Action~~

Pharmacodynamics

Please see comments provided by Clinical Pharmacology.

The information provided under Effect on Estrogens, Effect on Corticosteroids, and Other Endocrine Effects appear to accurately reflect the information found in Volume 2.9.

EXEMESTANE TABLETS NDA 20-753

ITEMS 13 & 14
PATENT INFORMATION AND CERTIFICATION

1.	Active Ingredient	exemestane
2.	Strengths	25 mg
3.	Trademark	Aromasin®
4.	Dosage Form Route of Administration	sugar coated tablets oral
5.	Applicant Firm Name	Pharmacia & Upjohn Company
6.	NDA Number	20-753
7.	Approval Date	to be determined
8.	Patent Information	exemestane is claimed per se in United States Patents 4,808,616 and 4,904,650 which currently expire July 7, 2006 and are subject to extension.
9.	Patent Certification	Applicant hereby certifies that exemestane is claimed per se in United States Patents 4,808,616 and 4,904,650 which currently expire July 7, 2006 and are subject to extension

Karin T. Weston. 8 Dec 1998

Karin T. Weston — Date
Regulatory Director

REQUEST FOR EXCLUSIVITY

Pharmacia & Upjohn company requests five (5) years of exclusivity for exemestane tablets pursuant to 21 U.S.C. 355(j)(4)(D)(ii). The following is provided to assist FDA in the eligibility determination. This summary information follows the basic format contained in the letter of April 28, 1988 from Dr. Carl Peck to All NDA or ANDA Holders and Applicants.

1. Whether any active moiety in the drug product for which approval is sought has ever been approved in another drug product in the United States either as single entity or as part of a combination product.

   Reply:
   Pharmacia & Upjohn Company certifies that the active moiety (exemestane) in the drug product for which approval is being sought has not been approved in another drug product in the United States either as a single entity or as part of a combination product.

2. If not, whether any active moiety of the drug product has been previously marketed in the United States, and under what name.

   Reply:
   Pharmacia & Upjohn Company certifies that the active moiety (exemestane) in the drug product has not been previously marketed in the United States.

Karin T Weston 22 Feb 99

Karin T. Weston
Regulatory Director

Date

EXCLUSIVITY SUMMARY FOR NDA # 20-753 SUPPL #_____

Trade Name Aromasin® Tablets Generic Name exemestane

Applicant Name Pharmacia & Upjohn HFD # 150

Approval Date If Known _____

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 question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

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

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 /X/ NO /___/

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

5 years

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8.

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 8 (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 /___/ NO /X/

APPEARS THIS WAY
ON ORIGINAL

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

NDA# _____ _____

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 /___/

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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /___/ 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 8:

_____

_____

(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 /___/

(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 /___/

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:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 YES /___/ NO /___/

Investigation #2 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:

_____ _____

_____ _____

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 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

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

IND # _____ YES /___/ 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 /___/

If yes, explain: _____

_____

/S/ 10/24/99

Signature Date

Title: Project Manager

/S/ 10/31/99

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20753	**Trade Name:**	AROMASIN (EXEMESTANE) 25MG TABS
Supplement Number:		**Generic Name:**	EXEMESTANE
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:		**Proposed Indication:**	treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The sponsor has received orphan drug designation and therefore, the Pediatric Rule does not apply. (AStaten, 9-22-99)

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANN STATEN

/S/ 9/22/99

Signature Date

DEBARMENT CERTIFICATION FOR NDA 20753, IND 36222

Exemestane

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Edward L. Patt

10/27/98

Ed L. Patt
Manager
Regulatory Compliance

Date

Slaten

OCT 14 1999

45-DAY MEDICAL REVIEW OF NDA 20-753

I. General Information

- Receipt Date: December 21 , 1998
- Drug: Aromasin® (Exemestane)
- Sponsor: Pharmacia & Upjohn
- Pharmacologic Category: Irreversible steroidal aromatase inhibitor
- Dose and administration: Sugar coated 25 mg capsule to be taken orally once a day

II. Proposed Indication

"AROMASIN Tablets are indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy. AROMASIN Tablets are also indicated for the treatment of postmenopausal women with advanced breast cancer whose disease has progressed following multiple hormonal therapies."

III. NDA Submission

The pivotal trial (94-OEXE-018): EXEMESTANE VERSUS MEGESTROL ACETATE IN POSTMENOPAUSAL PATIENTS WITH METASTATIC BREAST CANCER FAILING TAMOXIFEN: A PHASE III, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, COMPARATIVE STUDY.

A total of 769 patients were randomized (366 to exemestane and 403 to megace) at 144 (vs. 148?) centers worldwide from 10/27/95 to 8/31/98. The primary endpoint was response rate. Other endpoints were duration of response, TTP, TTF, survival, PS WOL, TRSS, safety, and effect of serum estrogen levels.

Supporting trials: Two Phase 2 trials in a similar patient population have been conducted. (1) Study 010 enrolled 140 patients and Study 120002 enrolled 129. Objective response rate is said to be 23 and 28%, respectively (responses did not undergo external review).

Volume 3.1 (Index); 3.2 (labeling); 3.3 (Summary); 3.9-3.91 (Section 8);
A CD containing ACCESS datasets
Electronic CRTs (Section 11) and CRFs (Section 12)

IV. Issues

- Although RR and SD are similar, sponsor claims a statistically significant improvement in TTP and survival for exemestane.
- Second indication. How much of a review needs to be done? Do efficacy data from these trials get into the label, or just safety via the ISS.

There are 3 Phase 2 trials contributing a total of 419 patients:

#12003	tam & megace failures	13.2% ORR
# 022	tam & megace failures	9.4% ORR
#017	aminoglutethemide & NSAI failures	6.6% ORR

Sponsor claims "long-term disease stabilization of $\geq$ 24 weeks in 17.5%" (however, these are uncontrolled trials).

- Discrepancy in number of patients per arm -- due to minimization procedure used to randomize patients?
- Shall we request the final summary in Word? Other than the label, I do not believe any text has been submitted electronically.

V. Audit Sites

The study was multinational, conducted in 19 countries, at 144 (vs 148?) sites. The largest accruing sites in descending order were:

There were 37 sites accruing 150 patients in the U.S.; however, only one site accrued $\geq$10 patients (site #417). In fact, this site represents a network. The site with the second largest group of patients in the U.S. is (site #420) where 9 patients were entered.

Recommendation: In addition to the two largest accruing centers in the U.S. (#417 and #420), we recommend that be audited. It is the single largest accruing center and is where the sponsor is located, i.e., there is a potential for bias.

VI. Consults

Under Mechanism of Action and Pharmacodynamics in the label, the effect of exemestane on estrogens, adrenal axis, and receptors, as derived from Phase I and 2 trials, is described. There are 11+ references to studies.

Do we want an M&E consult?

VII. Conclusion: NDA appears filable.

/S/
Alison Martin, M.D.

cc: Orig NDA 20-753
DD FILE
HFD-150 /Admin/Asst.

Memorandum

August 17, 1999

Subject: **NDA 20-753, Exemestane Tablets. Request for information.**

From: **Division of Pharmaceutical Evaluation I, OCPB, CDER, FDA**

To: **Applicant/Pharmacia & Upjohn Company**

It was noted that studies 95-OEXE-015 and 95-OEXE-016 are preliminary reports. Since the information to be provided by these studies are important both for review of the NDA and for the package insert, the final reports are required. Please provide the following information immediately.

1. The status of these studies.
2. Your 4-month safety update, which was censored in December of 1998, indicated that you have 6 volunteers and 12 patients treated in Study 95-OEXE-015. Please update your database and provide interim study report immediately.
3. The time line for submitting the final reports of these studies. When planning this, consider the time frame of the NDA review.

John Duan, Ph.D.

Reviewer, DPE1
OCPB, CDER

JAN 28 1999

45-DAY FILING REVIEW
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA 20,753	**Submission Date:** November 30, 1998
Drug Name:	Aromasin® (Exemestane, PNU-155971, FCE 24304)
Formulation % Strength:	Tablet, 25 mg
Sponsor:	Pharmacia & Upjohn Company Kalamazoo, MI 49001
Reviewer:	Lydia V. Kieffer, Pharm.D.
Type of Submission:	Presubmission of Section 6 of a New Drug Application

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Exemestane is an irreversible steroidal aromatase inhibitor. The sponsor is seeking two indications: 1) for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy, and 2) for the treatment of postmenopausal women with advanced breast cancer whose disease has progressed following multiple hormonal therapies. The proposed dose is 25 mg once daily.

Thirty-five studies have been submitted of which 21 are considered by the sponsor to be of most significance from the Clinical Pharmacology and Biopharmaceutics perspective. Of the 21 studies, 5 studies address analytical methods specifically and 12 studies are phase I trials. Dissolution data has been submitted.

Three different formulations and manufacturing processes were used throughout the development of the final product. As a result, an inspection by DSI will be requested of study 97-OEXE-035, the pivotal Bioequivalence study of the NDA. Complete details regarding study location, dates, etc. will be provided within 7 days of filing to DSI.

The Biopharmaceutics section of the NDA is indexed, paginated, and organized in such a manner as to facilitate review of the material.

Comments:

1. Was any pharmacokinetic data generated from the Phase III trial 94-OEXE-018? If so, please submit.

2. Besides hard copies, **all raw biopharmaceutic/pharmacokinetic data** contained in the NDA should be submitted in **electronic format** (ASCII or Microsoft EXCEL 5.0 for Windows, or formats readily converted to ASCII or EXCEL 5.0 by tools possessed by the Agency).

Recommendations:
The NDA 20,753 (Exemestane) is acceptable for filing from the Clinical Pharmacology and Biopharmaceutics perspective.

/S/ 1/28/99

Lydia V. Kieffer, Pharm.D.
Reviewer
Division of Pharmaceutical Evaluation I

/S/ 1/28/99

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

cc: Orig 20,753
HFD-150/ Division File
HFD-150/ ~~PStumm~~, AMartin, JBeitz, ~~AStarke~~
HFD-850/ LLesko
HFD-860/ MMehta, ARahman, LVelazquezKieffer
HFD-340/Vishwanathan
CDR BMurphy

TO: Dr. Anna Polli
Pharmacia & Upjohn

FROM: Clare Gnecco, Ph.D.
FDA/CDER
Division of Oncologic Drug Products

DATE: August 25, 1999

RE: Raw dates for duration calculations

We are progressing with our review of the Exemestane NDA application. To facilitate the review please provide a SAS file with all of the raw dates used to compute durations for all of the time to event variables for study #018. For ease of use it would be helpful if you could incorporate these into a file with all of the other relevant information needed to conduct time to event comparisons, e.g. treatment group indicator, censoring indicator, etc.

We have recently conveyed this request to your regulatory affairs group in the U.S. Your timely response would be greatly appreciated. If you have any questions, please do not hesitate to call or e-mail me directly. Thanks in advance.

TELECON MINUTES

MEETING DATE: May 7, 1999 TIME: 10:00 am

NDA 20-753

DRUG: exemestane tablets

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. Guidance

2. Proposed Indication: Advanced breast cancer in post-menopausal women whose disease has progressed following antiestrogen therapy

FDA PARTICIPANTS:
Dr. Clare Gnecco – Biometrics Reviewer
Mr. Patrick Guinn – Project Manager

INDUSTRY PARTICIPANTS:
Dr. Anna Polli – Biometrics
Dr. Nicoletta Orlando – Biometrics
Ms. Cecelia Blomqvist – Regulatory Affairs

MEETING OBJECTIVES:

To clarify what is required for submission, regarding the statistical information, in order for us to conduct our review of NDA 20-753.

DISCUSSION and DECISIONS REACHED:

1. Pivotal Study 018:

   - The SAS programs used to generate the major efficacy analyses in either hard copy, printouts or electronically should be submitted to the Division of Oncology Drug Products as soon as possible.

   - The SAS programming code for ANOVA modeling regarding the QOL should be submitted as soon as possible.

   - All other SAS data files not already submitted and necessary to reconstruct efficacy analyses should be submitted as soon as possible.

2. Study 17 and Study 22:

   - No inferential analysis was done. We need only the raw data if it has not already been submitted in the ACCESS database..

3. Communication:

   - It is acceptable for the Statisticians to contact each other directly in order to expedite clarification of issues. However, Patrick Guinn (FDA, Project Manager) and Cecelia Blomqvist (Pharmacia & Upjohn, Regulatory Manager) should be notified of any regulatory issues or any correspondences that need to be provided.

   - Dr. Anna Polli can be contacted as follows:
     Telephone: +39-02-4838-2074
     FAX: +39-02-4838-2249
     E-mail: anna.polli@cu.pnu.com

   - Dr. Clare Gnecco can be reached as follows:
     Telephone: 301-594-5739
     FAX: 301-827-4590 or 301-594-6593
     E-mail: gneccoc@cder.fda.gov

ACTION ITEMS:

1. The minutes will be finalized by Patrick Guinn (Project Manager – FDA) and forwarded to Pharmacia & Upjohn.

2. Pharmacia & Upjohn will provide the requested documentation in order for the FDA to have the ability to review the statistical information in support of NDA 20-753.

The meeting was concluded at 10:30 am. There were no unresolved issues or discussion points.

/S/
Patrick Guinn, Project Manager
Minutes preparer

Concurrence Chair: /S/
Clare Gnecco, Ph.D.
Biometrics Reviewer

TO: Dr. Anna Polli
Pharmacia & Upjohn

FROM: ~~Clare Gnecco, Ph.D.~~
Alison Martin, M.D.
Division of Oncologic Drug Products

DATE: September 3, 1999

RE: Additional dates request / minimization procedure information

---

Thank you very much for your timely response to our request for the augmented electronic dates file. We find that we will also need dates of randomization for study #018. Please provide a SAS file for this study with PATNO, CENTRE, TREAT_R, and date of randomization. We haven't been able to locate randomization dates in the electronic files submitted.

To complete our review of actual treatment allocation results achieved by the minimization procedure it would be helpful if you could provide the following information:

(1) Please confirm which countries requested treatment assignments by the U.S. minimization center and ~~which~~ requested assignments from the Milan center.
(2) Please explain how stratification by country interfaced with the minimization procedure.
(3) Please provide a copy of the Visual C++ program used to implement the minimization algorithm as well as representative samples (two or three consecutive ones) of the allocation tables from each of the minimization centers if these are still available.
(4) Please provide a copy of the SOP used by the two minimization centers.
(5) To get a more realistic picture of the expected degree of instability of the minimization procedure it is suggested that further simulation studies be carried out with smaller country sample sizes, say n = 5, 10, 20, 25, 50. Only two countries contributed 100 or more patients.

P. GUINN

MEETING MINUTES

MEETING DATE: March 24, 1999 **TIME:** 1:00 PM **LOCATION:** Conf. Rm. B

NDA: 20-753

Submission Date: December 21, 1998
UF Goal Date: October 21, 1999
Division Goal Date: September 21, 1999

DRUG: exemestane tablets

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. 3-month Team Meeting

2. Proposed Indication: Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following antiestrogen therapy and for the treatment of postmenopausal women with advanced breast cancer whose disease has progressed following multiple hormonal therapies.

FDA PARTICIPANTS:

Julie Beitz, M.D. - Medical Team Leader, Division of Oncology Drug Products
Alison Martin, M.D.; - Medical Officer
Rebecca Wood, Ph.D. – Chemistry Team Leader
Josephine Jee – Chemistry Reviewer
Paul Andrews, Ph.D. – Pharmacology Team Leader
John Leighton, Ph.D. – Pharmacology Reviewer
Atik Rahman - Clincial Pharmacology and Biopharmaceutics Team Leader
Emmanuel Fadiran, Ph.D. - Clincial Pharmacology and Biopharmaceutics Reviewer
Gang Chen, Ph.D. – Biometrics Team Leader
Clare Gnecco, Ph.D. – Biometrics Reviewer
Patrick Guinn -Project Manager

MEETING OBJECTIVES:

This meeting will be a monthly team update meeting. We will determine the Division goal date and which ODAC Meeting this application will be discussed. We will also decide when the labeling reviews should be completed and when we will start the labeling meeting process. We will also identify any issues/deficiencies that still need to be resolved.

DECISIONS REACHED:

- This application will be discussed at the September ODAC Meeting (tentatively September 16th and 17th) instead of the June ODAC Meeting as previously decided upon.

- Initial labeling reviews should be completed and provided to the Project Manager, Patrick Guinn, no later than July 13, 1999 to discuss labeling revisions at the July 20, 1999 Team Meeting.

- The following is a list of outstanding issues, listed by discipline:

  Medical: None

  Chemistry: Bottle and blister pack samples should be submitted.

  Pharmacology: None

  Statistics: Submission of electronic data was not provided.

  Biopharmaceutics: Study reports should be submitted electronically.

  Microbiology:

  DSI: Clinical Audits requested February 1, 1999
  PK Audits requested February 18, 1999

  Other: Team meetings are scheduled for April 19, May 24, June 18, July 20 (initial labeling), August 18, September 10 (ODAC Practice), and October 5, 1999.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION: None

This meeting concluded at 1:30 PM.

/S/

Patrick Guinn, Project Manager
Minutes preparer