

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-726**

**CORRESPONDENCE**

OCT 1<sup>5</sup>/<sub>2</sub> 1996

NDA 20-726

Ciba Pharmaceuticals Division  
Ciba-Geigy Corporation  
556 Morris Avenue  
Summit, New Jersey 07901

Attention: Adrian L. Birch  
Executive Director, Drug Regulatory Affairs

Dear Mr. Birch:

Please refer to your pending July 24, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Femara™ (letrozole tablets), 2.5 mg.

We have completed our review of the chemistry, manufacturing, and controls (CMC) section of your submission and have identified the following deficiencies.

- A. The following comments pertain to the drug substance:
1. The Assay specification for  
should be clarified.
  2. Please describe the synthesis and full characterization of a Reference Standard produced using the revised synthetic route.
  3. Specifications to be used to qualify current and future lots of drug substance Reference Standard should be submitted and justified.
  4. Clarification is requested whether the specifications listed in the Ciba Monograph are the regulatory specifications (i.e., shelf-life) or release specifications for the drug substance. In addition, please explain the following sentence which appears in the Ciba Monograph on p.007 Volume 3:
  5. Specifications and test methods for other organic residual solvents  
in the drug substance need to be developed  
and submitted.
  6. The specifications (i.e., criteria for conformance) for the Identification test should be better defined.

7. Specifications should be included for  

in the regulatory specifications

for the drug substance.
8. Purity profiles should be provided for several representative drug substance batches in support of the proposed regulatory specifications. The purity profile should be listed in a tabular format including the date of manufacture, production site, test date and level of all impurities and related substances. Levels of water, heavy metals, acetone, toluene, DMF, methanol and ethylacetate should be reported. Specifically, submit the full test data for Batch Nos. 800193, 800293, 800393, 800195, 800295 and 800395.
9. Full descriptions and acceptance specifications should be provided for the container/closure system used for the storage of the drug substance, including the name of the manufacturer.
10. Submit, for the plastic bags, the following information:
  - a. Composition; and
  - b. physicochemical test data (USP).This information may be provided by reference to the manufacturer's drug master file.
11. Please submit stability data for Batch Nos. 800195, 800295 and 800395 that were produced on May 18, 19 and 23, 1995 at the commercial production site.
12. It was recommended at the pre-NDA meeting that additional stress studies be conducted by increasing the storage temperature in increments until degradation is observed. This study will validate the analytical method used for the drug substance and drug product, as well as identify the potential degradants.
13. The proposed Stability Protocol for the drug substance should be submitted, including the storage condition and what tests will be performed at each test point.

B. The following deficiencies concern the drug product:

1. The following deficiencies concern excipients used in the drug product:
  - a. All excipients used in manufacturing the drug product must meet USP/NF specifications as required by the Food Drug and Cosmetic Act, Section 501(b) and Section 201(g)(1)(A) and (D).

- b. Indicate who performs testing of excipients.
  - c. The specification for \_\_\_\_\_ with \_\_\_\_\_% should be revised to include both an upper and lower limit for the percentage.
2. Specify an upper and lower limit for the batch size.
  3. Provide an executed (actual) batch production and control record for a representative batch used in a pivotal clinical study as well as one of the stability studies.
  4. Provide the proposed batch record to be used for commercial manufacturing of the drug product.
  5. Provide a description of the test methods for all of the in-process specifications.
  6. Provide the test results for in-process control testing performed on several representative batches of drug product in order to evaluate if the proposed specifications are reasonable.
  7. Provide information on the procedures used to sample the drug product for release testing.
  8. Provide a tabulation of release data for several representative drug product batches. These batches should have been produced on pilot or commercial scale using the proposed commercial process.
  9. It is suggested that the following tests and limits be included in the regulatory specifications: Moisture, Hardness, Residual Solvents (EtOH and I-PrOH), and Total Related Substances. Some of these tests may be eliminated in the future if analysis of release test results, for several commercial batches, of the drug product indicate that the tests are not necessary. In addition, tablet dimensions should be included in the specification for Appearance.
  10. Please clarify why the drug product specifications provided on page 9 of volume 5 differ from those provided on page 118 of volume 7 (specification for Dissolution, Enterobacteria, Content of CGS 20268 and Other Related Substances).
  11. The adequacy of regulatory specifications for the drug product will be judged after additional release test data and longer term stability data have been submitted for representative drug product batches.

12. The following deficiencies concern the presence of  
detected in drug product stored in HDPE bottles:
  - a. Provide experimental evidence to clearly establish that the impurities detected in the drug product stored in HDPE bottles are in fact
  - b. Provide data demonstrating that  
are in fact present in the HDPE bottles used to package drug product in which  
were detected.
  - c. Provide data to show whether  
are detected in drug product stored in the container/closure system proposed for use in the United States. If these impurities are observed, data need to be provided that  
are in fact present in the HDPE bottles that will be used to package drug product in the United States.
  - d. Provide data concerning the toxicity of
13. In validating the TLC and HPLC Identity test method, it should be demonstrated that degradation products from the drug substance do not interfere with the specificity of the test method.
14. The primary stability data provided in the original NDA submission are inadequate to support a 2 year expiration dating period with storage at room temperature. Please provide updated long term stability data for the drug product in the container/closure intended for marketing.
15. All stability protocols should include the following additional specifications: Appearance, Hardness, Moisture, and Total Related Substances. In addition, the stability protocol should include a specification for  
Also the stability protocol should include testing at the 1, 2, 3 and 6 months time points for the accelerated conditions of 40° C/75%RH.
16. Stability data should be provided in a tabular form with an individual table for each batch placed on stability. Each table should include the batch number, the manufacturer of the container/closure, the number of tablets per bottle, the lot of drug substance used to manufacture the batch of drug product, the date of manufacture for the drug product, and the date the drug product was placed into stability.

17. Provide a commitment to place into stability the first three commercial drug product batches in each proposed commercial container/closure system evaluating samples of the 30 and 100 counts.
18. Indicate who was the supplier of the 45 cc HDPE bottle used in the supporting stability studies. How does this container/closure differ from the container/closure intended for marketing?
19. On the bottle label, the established name should include the word  
The label should read:
20. In the DESCRIPTION section of the package insert references should be deleted. In addition, the inactive ingredients should be listed by their proper compendial name
21. In the HOW SUPPLIED section of the package insert, the packaging components should be described  
Additionally, the references should be deleted from the text.
22. Please provide actual samples of the bottle label.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Dianne Spillman  
Project Manager  
(301) 594-5770

Sincerely yours,

 10-11-96

Robert J. DeLap, M.D., Ph.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Office of Review Management  
Center for Drug Evaluation and Research

cc:

Original NDA 20-726

HFD-150/Div. Files

HFD-150/L.Zhou

HFD-150/P.Dietze

HFD-150/E.Tolgyesi

HFD-150/810//C.Hoiberg

HFD-150/CSO/D.Spillman/drafted: 10-7-96

HFD-80/DDIR

R/D initialed by: L.Zhou/10-8-96

P.Dietze/10-8-96

E.Tolgyesi/10-8-96

P.Zimmerman for D.Pease/10-10-96

F/T by: dds/10-10-96

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*ddspillman*  
10/11/96

**INFORMATION REQUEST (IR)**



Novartis Pharmaceuticals Corporation  
 Drug Regulatory Affairs  
 59 Route 10  
 East Hanover, NJ 07936-1080

Tel 201 503 7500  
 Fax 201 503 6325

July 14, 1997

NDA 20-726  
 Femara™  
 (letrozole, CGS 20267)

FDA Center for Drug Evaluation and Research  
 Office of Drug Evaluation I (HFD-150)  
 Document Control Room #20N  
 Woodmont FDA Oncology Drug Group  
 1451 Rockville Pike  
 Rockville, Maryland 20852-1448

Attention: Robert J. DeLap, M.D., Director  
 Division of Oncology Drug Products

Dear Dr. DeLap:

Reference is made to our Femara™ NDA 20-726, dated July 24, 1996 for the treatment of advanced breast cancer in postmenopausal women. Reference is also made to a fax received from Ms. Dianne Spillman on May 16, 1997 which provided Biopharm review comments, and our subsequent response dated June 16, 1997. At this time, we would like to provide a further response to the Biopharm reviewer's comments recommending an interim dissolution specifications. Additional timeline information regarding our Phase IV biopharm study commitments of July 9, 1997 is also provided.

As recommended in the May 16th fax, we will use the interim dissolution specifications recommended for Femara tablets (e.g. 75 rpm instead of 100 rpm). As previously stated in our June 16th response, we will also conduct the four additional dissolution profiles requested and submit this data for further evaluation of these specifications in September 1997.

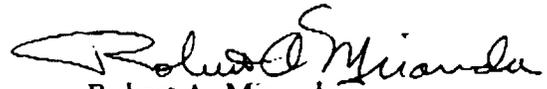
In our July 9th letter we committed to conduct the requested PK study in patients with severe hepatic impairment which is planned to start in 1Q98. Since we anticipate that recruitment of subjects with severe hepatic impairment will be difficult, the completion of this study will probably not be earlier than 4Q98.

Regarding our Phase IV commitment to conduct a drug interaction study between Femara and diazepam using in vitro techniques, we also stated in our July 9th letter that this study will start in 1Q98. We anticipate that completion of this study will be in 3Q98.

|                   |                |         |            |            |   |
|-------------------|----------------|---------|------------|------------|---|
| Post-it* Fax Note | 7671           | Date    | 7-14-97    | # of pages | 2 |
| To                | Diane Spillman | From    | R. Miranda |            |   |
| Co/Dept           |                | Co.     |            |            |   |
| Phone #           |                | Phone # | 57444      |            |   |
| Fax #             | (301) 827-4590 | Fax #   | 4751       |            |   |

If you have any questions or comments regarding this response, please contact me at (908) 277-5744.

Sincerely,



Robert A. Miranda  
Associate Director  
Drug Regulatory Affairs

RAM:sf



Novartis Pharmaceuticals Corporation  
Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

July 9, 1997

Tel 201 503 7500  
Fax 201 503 6325

**NDA 20-726**  
**Femara™**  
**(letrozole, CGS 20267)**

**NDA ORIG AMENDMENT**

FDA Center for Drug Evaluation and Research  
Office of Drug Evaluation I (HFD-150)  
Document Control Room #20N  
Woodmont FDA Oncology Drug Group  
1451 Rockville Pike  
Rockville, Maryland 20852-1448



Attention: Robert J. DeLap, M.D., Director  
Division of Oncology Drug Products

Dear Dr. DeLap:

Reference is made to our Femara™ NDA 20-726, dated July 24, 1996 for the treatment of advanced breast cancer in postmenopausal women. Reference is also made to a fax received from Ms. Dianne Spillman on May 16, 1997, which provided Biopharm review comments, and our subsequent response dated June 16, 1997. At this time, we would like to provide a further response to the Biopharm reviewer's comments recommending that we perform two additional studies as Phase IV commitments.

We understand that the Biopharm reviewer has evaluated our June 16th response and still recommends that the following two studies be conducted:

As recommended, we will agree to conduct the above studies as Phase IV commitments following the approval of our NDA. These studies are currently planned to be initiated during 1Q98.

If you have any questions or comments regarding this response, please contact me at (908) 277-5744.

Sincerely,

Robert A. Miranda  
Associate Director  
Drug Regulatory Affairs

DUPLICATE

RAM:sf

ORIGINAL

NEW CORRESP

 NOVARTIS

July 1, 1997

**NDA 20-726**  
**Femara™**  
**(Ietrozole, CGS 20267)**

NCI



FDA Center for Drug Evaluation and Research  
Office of Drug Evaluation I (HFD-150)  
Document Control Room #20N  
Woodmont FDA Oncology Drug Group  
1451 Rockville Pike  
Rockville, Maryland 20852-1448

Attention: Robert J. DeLap, M.D., Director  
Division of Oncology Drug Products

Dear Dr. DeLap:

Reference is made to our Femara™ NDA 20-726, dated July 24, 1996 for the treatment of advanced breast cancer in postmenopausal women. Reference is also made to the PI proposed by your Division and received from Ms. Dianne Spillman in a fax dated June 27, 1997. At this time we would like to discuss some concerns associated with this product labeling.

As you know, we received a first version of the Division's draft labeling on May 19th. After reviewing that initial draft, we identified some issues and provided our comments and counter-proposals in an annotated PI faxed to Ms. Spillman on June 4, 1997. It was our understanding that we would be able to discuss these issues with you and members of your staff in a meeting. Therefore, detailed explanations supporting our counter-proposals were not provided in writing. Our present concern is that we may not have the opportunity to have this discussion before an action letter is issued. The purpose of this letter is to explain some of the concerns we have with the PI currently being proposed by the Division.

Although the draft labeling from the Division is generally acceptable to us, we would like to resolve questions with the FDA datafiles received on June 27 with the reviewers. But more importantly, there are several issues which we believe puts us at a competitive disadvantage due to reviewing inconsistencies between Femara and Arimidex (sections I-III below). The following are the points and issues we would like you to consider. The line references used are from your latest PI received on June 27.

## I. ADVERSE REACTIONS:

- **Generally Well-Tolerated Statement (line 399)**

At the beginning of the Adverse Reactions section we propose the inclusion of an introduction statement, "Femara was generally well tolerated in two well-controlled clinical trials (i.e. Trials AR/BC2 and AR/BC3)." This statement is supported by data submitted to our NDA (e.g. discontinuations due to AEs, weight gain, thromboembolic events, etc.). In addition, the majority of adverse events were mild to moderate in severity and were usually related to the patient's metastatic breast cancer, the effects of estrogen deprivation, or to other intercurrent illnesses in this study population

This is also the same wording given to Arimidex, in its package insert, and we believe we presented comparable evidence to support this statement.

- **Patient Discontinuations due to AEs (line 412)**

There are a number of important discrepancies between the FDA's reported adverse events and those of the sponsor. We are particularly concerned about the differences in the reported number of discontinuations due to adverse events. The FDA listing of discontinuations (received 6/26/97) includes patients that discontinued due to progression of disease. We believe that these should not be considered adverse events and we believe this is inconsistent with how the data is presented in the Arimidex package insert.

We agree with the medical reviewer (fax dated June 26, 1997, point #2), that significantly fewer discontinuations occurred on the letrozole arms as compared to the megestrol arm, and this should also be included in this part of the labeling. There was a concern that treatment related discontinuations were not significant, however using the reviewer's numbers and pooling the Femara arms, the chi-square p-value is 0.047 and the Fisher's 2-tailed p-value is 0.056.

Therefore, we would like the following statement in the PI (line 414):

- **Weight Gain (AE Table following line 443)**

Our original proposed labeling included statistical results for weight gain from physical examinations. Due to current time constraints we are proposing to use weight gain results from adverse experience data which we can also justify as being statistically significant. The results are presented below and can be verified in data listings found in the NDA, and other previously submitted electronic files (i.e. 34S-AE Listings by patients; 15S-Investigator's Assessment of Disease Soft Tissue & Visceral: Lesion Measurements; 16S-Presence of New Lesions and Investigator's Assessment of Tumor Response).

We reviewed the 24 patients reflected in the adverse experience table for "weight increase" for AR/BC2, and determined that 6 patients had concomitant adverse events that were related to weight gain (e.g. pleural effusion, peripheral edema, ascites). The pooled Femara data caused less weight gain as compared to megestrol acetate (p=.021). To be consistent with the other pooled results presented in the PI (i.e. vaginal bleeding, thromboembolic events - lines 420-424), we propose the following sentence be added in line 424:

## **II. CLINICAL STUDIES / EFFICACY DATA:**

- **Significance of Duration of Response (lines 222, 244 table, 255 & 273 table)**

The median duration of response is mentioned on lines 219 and 253 of your proposed PI, but no statistics are included (see out deleted tables starting on lines 244 and 273). The current proposed PI also has no statement or statistics regarding duration of response and stable disease >=

In our counter-proposal PI we presented a summary of treatment comparisons for duration of response, and duration of response with stable disease >= (narrative and tables). We believe this is important information desired by the medical community. In prior discussions about fadrozole HCl (another aromatase inhibitor), FDA specifically requested we include duration of response in the analysis plan.

One concern we have is that the Division's package insert includes the median times for duration of response, but not the treatment comparison information (risk ratio, confidence interval, and p-value). As noted in the package insert, the median time for Femara 2.5 mg was not yet achieved. Adding the treatment comparison information (as presented in our package insert) will provide complete information about this endpoint for the physician. The treatment comparison p-value and confidence interval is based on the risk ratio and not the median. In this type of analysis, it is not necessary that median times be achieved, but only adequate number of failures be observed. Therefore, we propose that this endpoint be reflected as we propose in the final package insert.

- **Table Format (lines 244 and 273):**

We agree with the inclusion of the Kaplan Meier curves to show TTP results and believe this is important information to the prescribers. We also believe that the presentation of other efficacy data in a table format would also be helpful to prescribers because it is easier to read and compare results. The use of tables to supplement narrative descriptions is consistent with approved labeling for other types of anti-neoplastic drugs.

### III. CLINICAL PHARMACOLOGY / MECHANISM OF ACTION:

- (line 40)

In our original proposed labeling, we stated that \_\_\_\_\_, both in the Clinical Pharmacology and Animal Pharmacology sections. The PI describes the data which support these statements and references are contained in the original annotated PI. In the Division's first version of the PI, the references to \_\_\_\_\_ were deleted. In our counter-proposal we did not contest removal of the statement from the animal pharmacology section and further proposed to delete the word \_\_\_\_\_ in the only remaining statement in the Clinical Pharmacology section. This counter-proposal was not accepted in the Division's latest version of the PI.

We believe that the data referenced in the PI and submitted in our NDA supports the use of the terms \_\_\_\_\_ and this should be allowed to remain in the labeling. As you know, the Arimidex labeling contains an explicit statement that it is potent and selective under this section of their PI (i.e. "Anastrozole is a potent and selective nonsteroidal aromatase inhibitor."). We believe that not allowing us to include a similar statement, which is supported by our data, would unduly put us at a competitive disadvantage.

### IV. PRECAUTIONS / LABORATORY TESTS:

- **Increases in Liver Function Tests (line 332)**

We believe that the current Division proposed wording is confusing. It is stated that \_\_\_\_\_

Upon review of the database, it appears that there are proportionately more patients with elevations and no documented liver metastases in the other two treatments (megestrol 16/189 (8.5%) and AG 14/178 (7.9%). Therefore, we feel that it is inappropriate to highlight the specific incidence for Femara. Our proposed wording acknowledges this finding but also considers the other treatment arms

\_\_\_\_\_ We feel this wording more appropriately reflects the data.

### V. CARCINOGENESIS & IMPAIRMENT OF FERTILITY:

- **Benign Ovarian Stromal Tumors (line 367):**

The carcinogenicity study data presented for rats state (line 367) that it \_\_\_\_\_ We disagree with the statement that this is \_\_\_\_\_ The structure of this sentence

also leads one to believe that benign ovarian stromal tumors were seen at all dose levels when in fact the actual incidence presented in the NDA was 0/60 (controls), 0/60 (0.1 dose), 0/60 (1.0 dose), and 3/60 (10.0 dose). This is further supported by the Division PI wording on line 369 that states

Our suggestion for clarification would be to delete the statement on line 367 altogether because the more accurate statement appears later on line 369. An acceptable alternative would be to modify the existing statement on line 367 to read

- **Fertility Impairment in Male and Female Animals (line 377):**

This statement concerning results of fertility impairment on males and females is confusing because it tries to combine the results seen in two sexes for 3 species of animals, but only the females consistently showed the same changes. We propose deleting the data for males (due to relevance of indication) and rewording this section as follows:

If data must also be presented for males, we propose the following additional sentences:

In addition to the above issues and as mentioned early in this letter, we recently (6/27/97) received the electronic efficacy datafiles and are also concerned with data inconsistencies we have begun to identify. For example the p-value and confidence interval for TTP in AR/BC3 are inconsistent with each other [2.5/5, RR=.086 (.67, 0.93), p=0.24]. We are completing our review of these data files and we intend to identify any inconsistencies in a separate communication.

We understand that your current goal is to issue "approval" action letters, instead of "approvable" action letters whenever possible. We certainly welcome this strategy and want to facilitate the issuance of an approval letter, but we also wish to have the opportunity to review and/or discuss the final labeling in advance of receiving the action letter. It is currently unclear to us whether this will occur given the limited time until the PDUFA deadline.

As previously communicated to Ms. Spillman, and in the spirit of expediting the labeling review and the NDA approval process, we are most willing to discuss any of these labeling issues further with you.

If you have any questions or comments regarding this matter, please contact me at (908) 277-5744.

Sincerely yours,

Novartis Pharmaceuticals Corporation

A handwritten signature in black ink, appearing to read "Robert A. Miranda". The signature is fluid and cursive, with a large initial "R" and "M".

Robert A. Miranda  
Associate Director  
Drug Regulatory Affairs

RAM:sf

cc: Dr. Temple  
Ms. Spillman

 **NOVARTIS**

**ORIGINAL**

Novartis Pharmaceuticals Corporation  
Drug Regulatory Affairs  
59 Route 10  
East Hanover, NJ 07936-1080

Tel 201 503 7500  
Fax 201 503 6325

**NDA ORIG AMENDMENT  
(BL)**

June 26, 1997

**NDA 20-726  
Femara™  
(letrozole, CGS 20267)**

FDA Center for Drug Evaluation and Research  
Office of Drug Evaluation I (HFD-150)  
Document Control Room #20N  
Woodmont FDA Oncology Drug Group  
1451 Rockville Pike  
Rockville, Maryland 20852-1448



Attention: **Robert J. DeLap, M.D., Director**  
Division of Oncology Drug Products

Dear Dr. DeLap:

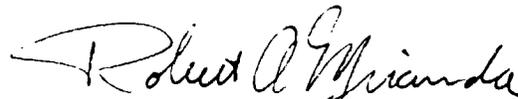
Reference is made to our Femara™ NDA 20-726, dated July 24, 1996 for the treatment of advanced breast cancer in postmenopausal women. At this time we would like to provide actual product bottle labels as requested by Ms. Dianne Spillman.

We have attached three sets of Femara bottle labels for your convenience. This label represents the final bottle label for Femara. A bottle carton is not used, therefore there is no carton label.

If you have any questions or comments regarding this submission, please contact me at (908) 277-5744.

Sincerely yours,

Novartis Pharmaceuticals Corporation



**Robert A. Miranda**  
Associate Director  
Drug Regulatory Affairs

RAM:sf  
enclosure