

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: NDA 20-726/S-006

CORRESPONDENCE

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Robert Miranda
From: Ann Staten, Project Manager

Fax: 973-781-6325
Fax: 301-827-4590

Phone: 973-781-2282
Phone: 301-594-5770

Pages: 21
Date: January 10, 2001

Re: NDA 20-726/006 Femara™ (letrozole) Tablets – Approval Letter

Urgent For Review Please Comment Please Reply Please Recycle

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

● **Comments:**

Bob,

Attached is the approval letter signed today by Dr. Pazdur. The electronic signature page follows the enclosure.

Sincerely,

Ann

/S/

cc: orig NDA 20-726
DIN FILE - HFD-150

Robert A. Miranda
Associate Director
Drug Regulatory
Affairs

Novartis Pharmaceuticals Corporation

Tel 973/781-2282
Fax 973/781-6325
Internet: robert.miranda
@pharma.novartis.com



Fax

Attention **Ms. Ann Staten**
FDA
Division of Oncologic Drug Products (HFD-150)
Rockville, MD

Fax no. **301/827-4590**
Number of pages **1 including cover page**

Date **January 10, 2000**

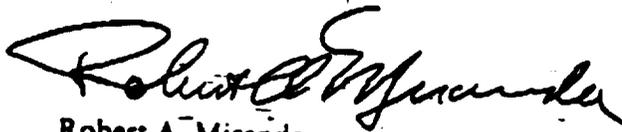
Concerning **Femara® NDA 20-726**
RE: Package Insert
Dear Ann,

Reference is made to our telecon today and the version of the package insert received today.

The version of the package insert received today is acceptable.

Thank you very much for all your assistance and we look forward to the final action letter.

Sincerely yours,


Robert A. Miranda

CC: **Orig NDA 20-726/006**
HFD-150 DIV FILE

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Robert Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: December 7, 2000

Re: NDA 20-726/006 Femara™ (letrozole) Tablets – 120 day safety update

Urgent For Review Please Comment Please Reply Please Recycle

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

● **Comments:**

Bob,

The medical officer has confirmed that a 120 day safety update is not necessary for this application.

Sincerely,

/S/

Ann

cc: orig NOA 20-726
DIV FILE
HFD-150 / A Staten

NOVARTIS

DUPLICATE

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

tel. 973 781 8300

October 25, 2000

Copy for NDA 20-726

IND No. _____

Femara (letrozole tablets)

- Response to FDA Request for Information
- Request for Meeting

Serial No. 237

NDA SUPP AMEND

SEI-006

BS



Richard Pazdur, MD
Director
Division of Oncology Drug Products/
HFD-150
Food and Drug Administration
Center for Drug Evaluation and
Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Pazdur:

Reference is made to our original NDA 20-726 and Supplement S-006, dated June 11, 2000 for Femara® (letrozole tablets). This supplemental NDA (sNDA) provides for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer. Reference is also made to a fax dated October 20, 2000 from Ms. Ann Staten. This fax reiterated a previous request for submission of survival data from study 025. We also make reference to a teleconference between Novartis and the Division on October 23, 2000 to discuss the content of the submission. At this teleconference, it was agreed that the survival data from the March 2000 cut-off would be provided immediately, and that the forthcoming update (October 2000 cut-off) would be provided as soon as possible. The variables for inclusion in the SAS Transport file were also discussed and agreed. To expedite review of the existing (March 2000) information, Novartis also agreed to provide the results of the statistical analysis conducted as well as the Kaplan-Meier curves (copy via fax also to Ann Staten).

A copy of this coverletter only is being provided to the NDA files.

At the teleconference on October 23, 2000, Novartis also mentioned the need to organize an additional teleconference to discuss inclusion of the survival data in the advisory committee package. We would like to formalize this request, and confirm that October 31, 2000 at 11:00am as you proposed would be acceptable. We will contact Ann Staten separately with the telephone number to contact us for that meeting.

Richard Pazdur

Page 2

IND No.

If you have any questions or comments regarding the sNDA, please contact Mr. Robert Miranda at (973) 781-2282.

Sincerely,



Paul Gallo, Ph.D.
Assistant Director, Biostatistics

Attachments: Floppy Disk (SAS Transport File of March 2000 Survival Data)
Kaplan Meier Plot of March 2000 Survival Data (incl. table of supporting data)
Log Rank Analysis of Survival for ITT Population

Copy of Coverletter Only to NDA 20-726 -
Desk Copy: Ann Staten (via Fax)

NOVARTIS

DUPLICATE

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

Tel 973 781 7500
Fax 973 781 6325

APPEARS THIS WAY
ON ORIGINAL

October 19, 2000



NDA SUPP AMEND
SEI-006
BM

NDA No. 20-726
(S-006)

Femara® (letrozole tablets)

OTHER: RESPONSE TO
MEDICAL INFORMATION
REQUEST

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Pazdur:

Reference is made to our original NDA 20-726 and Supplement S-006, dated June 11, 2000 for Femara® (letrozole tablets). This supplemental NDA (sNDA) provides for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer. Reference is also made to two faxes dated September 18, 2000 and October 10, 2000 from Ms. Ann Staten. These faxes requested additional information from the medical reviewer and are detailed below. At this time we would like to respond to these faxes.

In the September 18th fax the medical officer requested the following:

"Please provide the latest data available on the following parameters for patients enrolled in study 025:

- Overall survival
- Fractures
- Cerebral arterial events
- Coronary artery events (MI, angina)

In providing the above data please include all events, whether or not they were classified as cancer or non-cancer related. If there is data from other supporting studies that address the frequency of the above events please provide it."

- **Overall Survival**

At the time of the data cut for the primary analysis in study 025 (March 8, 2000), 304 patients overall in the ITT population had died. An external data monitoring committee (DMC) was convened after the results of the planned analysis of the core data were available as described in Protocol Amendment 4. The overall conclusions from the review of this interim analysis by the DMC were that the relative treatment effects on survival were not mature and that these survival results could be particularly misleading regarding the longer-term treatment effects. Therefore, the DMC recommended that this survival data not be divulged.

As determined by the DMC, it was decided that the committee would meet again approximately 6 – 9 months after the first interim analysis of survival (March 8, 2000). Survival will be updated as of October 16, 2000. This second interim analysis will be blinded to Novartis except for a statistician not associated with the project. The DMC plans on meeting to review these data on November 10, 2000 and if the analysis shows a significant difference and the data is considered mature, the second interim analysis along with the recommendations of the DMC will be sent immediately to the Agency and the Oncology Drug Advisory meeting. It is our understanding that survival data is not required for approval of this indication.

- **Fractures**

Our review of the databases for Protocol 25 revealed a total of 82 fractures from the entire study database (core and crossover). The majority of these events are related to bone metastasis. Fourteen (14) patients had fractures only at baseline. In the core phase, 54 patients reported fractures during their first line treatment (28 on tamoxifen, 25 on Femara, and 1 on combination therapy). During the crossover phase (ongoing, data cleaning in progress), 14 patients were reported to have had fractures (9 on tamoxifen and 5 on Femara).

Fractures were identified on the clinical database from tumor assessment, adverse events and comments or in the Global Safety Database (GDSS) for serious events. The following information is attached.

- Listing of preferred terms from MedDRA used to identify fracture events
- Table of fracture events
- Data listings for tumor findings, adverse events and comments from the clinical database for each patient reporting fracture (see RTF files in CD ROM)

In our completed second-line studies, comparable numbers of fracture were reported for Femara and its comparators (megestrol acetate and aminoglutethimide). Please refer to Femara IND submissions dated August 25, 1997 (Serial No. 181) and April 7, 1998 (Serial No. 196) for details of this second-line fracture data.

- **Cardiovascular Events (cerebral and coronary artery events)**

Cardiovascular events (myocardial infarction, angina) and cerebral arterial events were identified in the clinical database from adverse events and comments or in the GDSS database.

In summary, 31 patients reported cardiovascular events either directly identified as myocardial infarction or angina or as possibly related to these 2 terms by similar terminology. During the core phase, 13 tamoxifen and 15 Femara patients reported these types of events. In the crossover phase 3 tamoxifen patients reported cardiovascular events.

Cerebral arterial events during the core phase were reported in 27 patients (9 tamoxifen, 12 Femara, and 1 combination therapy). In the crossover phase these cerebral arterial events were reported in 1 Femara patient, and during the follow-up phase in 1 tamoxifen and 3 Femara patients.

The following information is attached for the cardiovascular and cerebral arterial events:

- Listing of preferred terms from MedDRA used to identify cardiovascular and cerebral arterial events
- Table of cardiovascular events
- Table of cerebral arterial events
- Data listings for adverse events and comment from the clinical database for each patient (see RTF files in CD ROM)

In the October 10th fax the medical officer requested the following:

"Please provide the latest safety data available on the following parameters for patients enrolled in study 025:

- by age and
- by ethnicity (if there is a significant non-Caucasian study population)

We need safety data broken down by those variables in addition to overall tabulation of safety data."

- **Age**

Safety data by age is provided in Post-text Table 10.1-1(age) in the attached CD-ROM as a RTF file. Grouping by age was done by the following categories: ≤ 55 , >55 to <70 , and ≥ 70 . Review by age group reveals an overall balance by age and by treatment group.

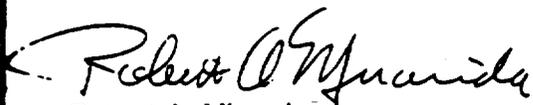
- **Ethnicity**

The population of the trial overall was 86% Caucasian, 3 % Black and 11% Oriental/Other. Safety data by ethnicity is provided in Post-Text Table 10.1-1(race) in the attached CD-ROM as a RTF file. Grouping by race was done by the following categories: Caucasian, Black and Oriental/Other. The Other category patients were predominately from India. The category of Black only includes 25 patients. Review by ethnicity group does not reveal any differences by treatment group although the small numbers of non-Caucasian patients limits any definitive conclusions.

The files being provided in the CD-ROM were scanned for viruses using Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

If you have any questions or comments regarding this sNDA, please contact me at (973) 781-2282.

Sincerely,



Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments: Tables
CD-ROM

Desk Copy via fax (without attachments): Ann Staten (HFD-150)

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Robert Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: October 10, 2000

Re: NDA 20-726/006 Femara™ (letrozole) Tablets – RE: 10-5-00 120-day safety update proposal

Urgent For Review Please Comment Please Reply Please Recycle

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

● Comments:

Bob,

The medical officer has looked at your proposal and does not want the blinded information.

Thanks,

/S/

Ann

cc: Orig NDA 20-726
Div File
HFD-150 / Astaten

Staten

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Robert Miranda **From:** Ann Staten, Project Manager

Fax: 973-781-6325 **Fax:** 301-827-4590

Phone: 973-781-2282 **Phone:** 301-594-5770

Pages: 1 **Date:** October 10, 2000

Re: NDA 20-726/006 Femara™ (letrozole) Tablets – medical information request

Urgent For Review Please Comment Please Reply Please Recycle

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

● **Comments:**

Bob,

The medical officer has the following information request:

Please provide the latest safety data available on the following parameters for patients enrolled in study 025:

1. by age and
2. by ethnicity (if there is a significant non-Caucasian study population)

We need safety data broken down by those variables in addition to overall tabulations of safety data. Hopefully you can send this ASAP.

Thanks,

/s/
Ann

cc orig NDA 20-726
Div FU
HFD-150/AnnStaten
-
McCohen

NOVARTIS

DUPLICATE

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

Tel: 973 781 7500
Fax: 973 781 6325

NDA SUPPLEMENT
SEI-006
SNC

October 5, 2000



NDA No. 20-726
Femara® (letrozole tablets)

OTHER: 120-DAY SAFETY
UPDATE PROPOSAL
(S-006)

New Indication:
(First-line treatment of
postmenopausal women with
advanced breast cancer)

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Pazdur:

Reference is made to our original NDA 20-726 and Supplement S-006, dated June 11, 2000 for Femara® (letrozole tablets). This supplemental NDA (sNDA) provides for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer. Reference is also made to the required safety update that is due four months after the initial submission. At this time we would like to submit our proposal for complying with this 120-day safety update and seek your agreement.

We propose to submit a safety update by November 12, 2000 covering the period of March 8 through Sept. 8, 2000 (6-months of new safety data). This safety report will update the tolerability and safety of Femara for the new indication, and include the same kinds of information as previously provided in the integrated summary of safety. The data from the first-line study Protocol 025, will be presented, plus all serious adverse events (SAEs) reported to Novartis from other completed studies in breast cancer since the Integrated Safety Summary (ISS) (refer to the table attached).

The SAEs reported in breast cancer
The

Safety data from P025 will consist of the following:

- All adverse events reported on the Case Report Form (CRF) during the core phase since the March 8, 2000 cutoff date
- All serious adverse events with an onset during the core phase of the study since March 8, 2000, or within 6 weeks of stopping trial treatment (or crossing to the alternative treatment) reported according to expedited procedures to the Novartis Safety Desk as of cutoff date March 8, 2000.
- All deaths occurring on core trial treatment since March 8, 2000 or within 6 weeks of stopping trial treatment (or crossing to the alternative treatment as of the cutoff date of March 8, 2000), and
- All laboratory data stemming from the core phase of the study since March 8, 2000

Overall, the above information will be available from approximately 111 women treated with letrozole 2.5 mg, and 67 with tamoxifen (patients remaining on the core study as of March 8, 2000). CRFs will be provided electronically as previously defined for the sNDA.

Presently there are approximately postmenopausal women treated in adjuvant or chemo-prevention trials under double-blind conditions. An estimated 50% of them are receiving letrozole 2.5 mg. In addition,

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,



Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356H
Table

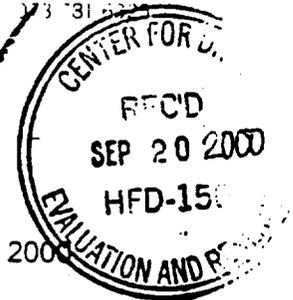
Desk Copy via fax: Ann Staten (HFD-150)

NOVARTIS

DUPLICATE

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

Tel: 973 981 7500
Fax: 973 981 6225



NDA SUPP AMEND
SEI-006
BM

September 19, 2000

NDA No. 20-726
Femara® (letrozole tablets)

MINOR AMENDMENT TO A
PENDING APPLICATION (S-006)

New Indication:
(First-line treatment of
postmenopausal women with
advanced breast cancer)

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Pazdur:

Reference is made to our original NDA 20-726 and Supplement S-006, dated June 11, 2000 for Femara® (letrozole tablets). This supplemental NDA (sNDA) provides for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer. Reference is also made to a fax dated August 29, 2000 from Ms. Ann Staten, which identified one table in the SAS transport datasets for the pivotal study (Table VVSI) as being incomplete. At this time we would like to respond to this fax and provide the corrected data.

In follow-up to the fax dated August 29th we checked and confirmed that the data in Table VVSI as originally provided was correct but not complete. It did not contain data beyond patient 0001_06110. As a result, we have conducted another QA check of all the SAS datasets previously provided and can confirm that all the datasets are correct and complete with the exception of two tables which contained missing data. These were tables VVSI (as previously discussed) and FORMATS (file was empty). The discrepancy with these tables had inadvertently occurred when we copied the data from one source file to another to prepare the original sNDA submission.

The complete tables VVSI and FORMATS are now being provided on the attached CD ROM for your use in updating the electronic data in our sNDA. Please note that I discussed this proposal with Randy Levin, Electronic Reviews (HFD-1) on September 15, 2000 and he agreed that the re-submission of the two files would be sufficient to amend the existing electronic data on file. The files being provided were scanned for viruses using Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

We apologize for any inconvenience this may have caused.
If you have any questions or comments regarding this sNDA, please contact me at
(973) 781-2282.

Sincerely,

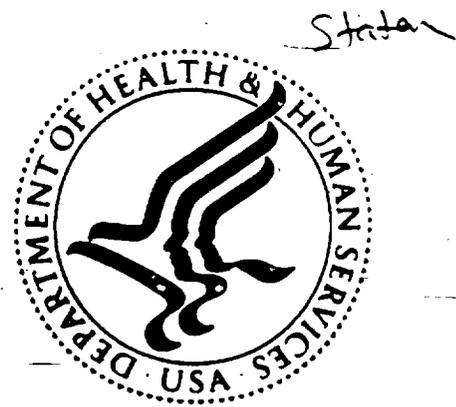


Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356H
CD-ROM

Desk Copy via fax (without CD-ROM): Ann Staten (HFD-150)

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Robert Miranda
From: Ann Staten, Project Manager

Fax: 973-781-6325
Fax: 301-827-4590

Phone: 973-781-2282
Phone: 301-594-5770

Pages: 1
Date: September 18, 2000

Re: NDA 20-726/006 Femara™ (letrozole) Tablets – medical information request

Urgent For Review Please Comment Please Reply Please Recycle

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

● **Comments:**

Bob,

The medical officer has the following information request:

Please provide the latest data available on the following parameters for patients enrolled in study 025:

1. overall survival
2. fractures
3. cerebral arterial events
4. coronary artery events (MI, angina)

In providing the above data please include all events, whether or not they were classified as cancer or non-cancer related.

If there is data from other supporting studies that address the frequency of the above events please provide it.

Thanks,

151

CC: Orig NDA 20-726
DIV FILE
- HFD-150 / AStaten

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Robert Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 2

Date: September 14, 1999

Re: IND [redacted] Femara™ (letrozole) Tablets; letter dated Sept. 1, 1999; Serial no. 219

Urgent For Review Please Comment Please Reply Please Recycle

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

● Comments:

Please refer to your protocol amendment for study No. 2026701025 submitted September 1, 1999 (serial no 219).

The Medical Officer has completed the review of this submission and has the following comments:

This amendment proposes 7 protocol modifications. All are satisfactory except for the definition of Time to Progression (TTP).

The sponsor's definition of TTP is:

- appearance of a new lesion, or increment $\geq 25\%$ of measurable lesion or progression in evaluable or unmeasurable, non-evaluable disease
- termination of core therapy with documented evidence of clinical deterioration due to breast cancer at the time of discontinuation

cc: orig IND [redacted]
Div File
HFD-150/Asstater/MLohrer

September 14, 1999

- death due to breast cancer or death of unknown cause while on study drug (core) or within 6 weeks of discontinuation. For death due to unknown cause, there must be documented evidence of clinical deterioration due to breast cancer.

Time to progression is right-censored if any of the following conditions apply at cutoff for analysis:

- Receiving trial treatment without evidence of progression
- Deaths from non-cancer causes
- Deaths of unknown cause without evidence of clinical deterioration due to breast cancer
- Discontinuation of core therapy (or crossover to the alternative therapy) without evidence of clinical deterioration due to breast cancer prior to discontinuation and no death due to breast cancer in the 6 weeks following discontinuation.

The end-date for TTP analysis will be the earliest date of documented progression of disease (visit date). In the absence of a clear diagnosis of progression, the end-date for TTP will be the date of the last clinical visit or previous tumor assessment (visit date) if the tumor assessment at the last clinical visit is incomplete. The exception to this would - be in the case of death or termination without tumor assessment, then the date of death or date of last contact respectively will be used. For cases where there is documented clinical deterioration of general condition due to breast cancer, or death of unknown cause with documented clinical deterioration due to breast cancer the date of the earliest visit at which the deterioration is documented will be taken.

FDA Interpretation

The problem with the above definition is that progression can be based on "clinical deterioration". Clinical deterioration is not defined. Further, it is difficult to imagine how clinical deterioration due to cancer could occur in the absence of objective evidence of disease progression. Also, in the FDA experience, cancer related clinical deterioration does not occur acutely so that investigators who suspect disease progression should have sufficient time to document that progression.

The FDA believes that in the absence of documented tumor progression patients who leave the study for any reason should be censored on the date of their last complete evaluation for progressive disease.

Please let me know if you have any questions.

Sincerely,

Ann

/s/

 **NOVARTIS**

ORIGINAL

Hilary A Chaudri-Ross
MA (Hons), DEP, CStat, ECPM
Senior Biostatistician

Novartis Pharma AG
WSJ-27.2.023, Postfach, CH-
4002 Basel, Switzerland

Tel +41 61 324 3280
Fax +41 61 324 3039
Internet: hilary_anne.chaudri
@pharma.novartis.com

Ann Staten, Project Manager
FDA - Div. Oncology Drug Prod.
Center for Drug Evaluation and
Research, HFD-150
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857, USA

NDA SUPP AMEND
SEI-006
BM



August 30, 2000

NDA 20-726/006 Femara™ (letrozole) Tablets, vvsi dataset

Dear Ms Staten,

My DRA colleague, Dr Robert Miranda, forwarded to me your fax dated August 29, concerning an incomplete dataset. I enclose a diskette containing 2 transport files,) and the other created with

Both files are self-extracting zipped files and will be extracted by activating the file. I also enclose for convenience a short description of the contents of the file.

I would appreciate it if you could forward the diskette and pages of description to the medical reviewer.

Yours sincerely,

Novartis Pharma AG

H. A. Chaudri

H A Chaudri
Project Statistician

DUPLICATE

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

August 31, 2000

*NAI
A. Staten
9-6-00*



NDA No. 20-726
Femara® (letrozole tablets)

GENERAL CORRESPONDENCE
TO PENDING APPLICATION
(S-006)

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

New Indication:
(First-line treatment of
postmenopausal women with
advanced breast cancer)

SUPL NEW CORRESP
SNC to
SEI-006

Dear Dr. Pazdur:

Reference is made to our original NDA 20-726 and Supplement S-006, dated June 11, 2000 for Femara® (letrozole tablets). This supplemental NDA (sNDA) provides for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer. At this time we would like to confirm the results of the 45-Day Filing Meeting for this supplement.

This confirms my telecon with Ms. Ann Staten, Project Manager on August 31, 2000. Ms. Staten stated that the 45-Day Filing Meeting had taken place for Femara S-006 and the following decisions were made:

1. NDA 20-726, S-006 was accepted for filing
2. NDA 20-726, S-006 was assigned a priority review, which means a 6-month review period.
3. Review by the Oncology Drugs Advisory Committee (ODAC) is not planned.

Please notify me immediately if the above understanding is not correct.

Thank you for your assistance. If you have any questions or comments regarding this sNDA, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachment: Form FDA 356H

Desk Copy: Ann Staten (HFD-150)

Chad

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Robert Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: August 29, 2000

Re: NDA 20-726/006 Femara™ (letrozole) Tablets

Urgent For Review Please Comment Please Reply Please Recycle

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

● **Comments:**

Bob,

The medical officer has identified that the electronic reviewer aide (CD-ROM in volume 5 under the clinical section) does not contain information in Table VVSI beyond patient 0001_06110.

Could you send a copy of the SAS transport files on a floppy disk directly to our division?

Thanks,

/s/
Ann

cc: orig NDA 20-726
Div File
HFD-150/Astaten

NOVARTIS

DUPLICATE



August 9, 2000

NDA No. 20-726
Femara® (letrozole tablets)

MINOR AMENDMENT TO A
PENDING APPLICATION (S-006)

New Indication:
(First-line treatment of
postmenopausal women with
advanced breast cancer)

NDA SUPP AMEND
S-006
BB

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Pazdur:

Reference is made to our original NDA 20-726 and Supplement S-006, dated June 11, 2000 for Femara® (letrozole tablets). This supplemental NDA (sNDA) provides for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer. At this time we are providing a Section 6, Human Pharmacokinetics and Bioavailability for our sNDA, which concentrates on the bioequivalency testing of the comparator drug used in our pivotal trial. This was done per a previous agreement.

On May 29, 1996 (IND [redacted] Serial 151) Novartis requested the use of a generic tamoxifen formulation (Tamofen® manufactured by Leiras Oy of Finland) to be used as the comparative agent in the large first-line and adjuvant international studies. In a subsequent FDA letter dated June 25, 1996, the use of this generic tamoxifen was deemed acceptable provided a bioequivalency study was conducted. The bioequivalence study report (Protocol 102) comparing Tamofen to the US approved formulation (Nolvadex) is now complete and is provided in the attached sNDA Section 6.

As you know, on May 16, 2000 (IND [redacted] Serial No. 232) Novartis requested permission to file sNDA (S-006) early without waiting for Study Report P102. In a FDA fax dated June 28, 2000, it was agreed that we could do this provided that Study Report P102 was submitted within 30 days of the sNDA filing. The current submission fulfills this agreement.

The PK raw data for study P102 is also provided electronically in accordance with agreements reached. This raw data is provided as Excel files (version '97) and is contained in the diskette provided in this submission. Please note that these files were scanned for viruses using Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

In addition to Study Report P102, new PK data since the original NDA is summarized in the sNDA Section 6 attached. Any reports referenced are provided or cross-referenced to previous submissions in our IND [redacted] or NDA 20-726.

Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent.

If you have any questions or comments regarding this sNDA, please contact me at (973) 781-2282.

Sincerely,



Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356H
Volumes 1-4

Desk Copies (2): Ann Staten (HFD-150)



Food and Drug Administration
Rockville MD 20857

NDA 20-726/S-006

JUL 17 2000

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Attention: Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Dear Mr. Miranda:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Femara® (Letrozole Tablets)

NDA Number: 20-726

Supplement Number: S-006

Date of Supplement: July 11, 2000

Date of Receipt: July 12, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 10, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

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

(if via courier)

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

Sincerely,

7/17/00

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

NDA 20-726/006
Page 2

cc:

Original NDA 20-726/006
HFD-150/Div. Files
HFD-150/CSO/A. Staten

SUPPLEMENT ACKNOWLEDGMENT

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Robert Miranda From: Dianne Spillman for Ann Staten

Fax: (973) 781-6325 Fax: (301) 594-0499

Phone: (973) 781-2282 Phone: (301) 594-5746

Pages (including cover): 1 Date: July 11, 2000

Re: IND [redacted] sn 232 - Division comments on request for sNDA filing prior to BE study report

Urgent For Review Please Comment Please Reply Please Recycle

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

Comments:

Bob:

Please refer to your discussion with Dotti Pease on June 23, 2000 and her subsequent fax on July 28, 2000 regarding the issue above. Following are the comments from the Clinical Pharmacology and Biopharmaceutics review of amendment #232, dated May 16, 2000.

1. The bioequivalence ties to be established based on the agreement reached at the beginning of the development program in 1996 (Submission serial No. 151 dated May 29, 1996 and subsequent FDA letter dated June 25, 1996).
2. Since the bioequivalence study will contribute a part of the filing issue for the supplemental NDA, you are required to submit the study report (with raw data and detailed assay validation data) within 30 days of the supplemental NDA submission.

If you have any questions regarding these comments, please contact Ann Staten at (301) 594-5770. She will return to the office starting Monday, July 17, 2000.

Sincerely,

/s/
Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: IND [redacted] sn 232 (GC)
HFD-150 Adv File # / A Staten
J. Owen / M. Cohen

 **NOVARTIS**



July 11, 2000

NDA No. 20-726 / S-006
Femara® (letrozole tablets)

SPECIAL SUPPLEMENT-
CHANGES REQUIRING PRIOR
APPROVAL

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

New Indication:
(First-line treatment of
postmenopausal women with
advanced breast cancer)

Dear Sir/Madam:

Reference is made to our NDA 20-726 for Femara® (letrozole tablets) approved for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy. At this time Novartis Pharmaceuticals Corporation submits a supplemental New Drug Application (sNDA) for a new indication in the first-line treatment of postmenopausal women with advanced breast cancer.

As you know, Femara is a potent third generation nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis). In a large adequate and well-controlled study in over 900 patients, Femara has been shown to be safe and effective in the treatment of postmenopausal women with advanced breast cancer. The efficacy data from this pivotal study and the other supportive studies are presented in this sNDA. Safety data in about 1300 patients from the pivotal study and supportive studies are presented and concludes that the overall safety profile of Femara is similar to that of tamoxifen in first-line treatment.

The Femara dose and schedule used for the new indication is the same as previously approved. Therefore, there is no new preclinical and only limited technical information in this sNDA.

This sNDA has been prepared in a manner that is consistent with existing regulations, relevant guidelines, and understandings that were reached at our pre-sNDA meetings on September 29, 1999 and subsequent correspondence dated October 13, 1999 (IND [redacted] Serial No. 223), February 1, 2000 (IND [redacted] Serial No. 228) and May 16, 2000 (IND [redacted] Serial No. 232). A copy of relevant correspondence is located in Volume 1 of the sNDA.

Request for Priority Review

We believe that this application qualifies for priority review according to CDER's MAPP 6020.3 in that Femara offers a significant improvement compared to marketed products, as a first-line treatment of post-menopausal women with advanced breast cancer. Femara has demonstrated with its clear and robust superior efficacy results over tamoxifen that this constitutes a significant improvement for the treatment of postmenopausal women with this serious and life-threatening disease.

A formal request for priority review of this sNDA was previously submitted to IND [redacted] on May 16, 2000 (Serial No. 232).

Electronic Sections and Reviewer Aids

As proposed in our pre-sNDA meeting of September 29, 1999, subsequently revised on April 28, 2000 (IND [redacted] Serial No. 231), and finally agreed with FDA (fax dated June 6, 2000), this submission includes the following sNDA components in electronic form:

Section 2: Annotated Package Insert – provided as an MS Word file on diskette in volume 1

Section 3: Overall NDA Summary – provided on a CD-ROM in volume 5

Section 8: Clinical Data – provided on a CD-ROM in volume 5

- Controlled Clinical Studies
 - Complete report and appendix 1 for the pivotal study (025)
 - Complete report for supportive controlled study (012)
- List of INDs/NDAs and Investigators
- Integrated Summary of Effectiveness (ISE)
- Integrated Summary of Safety (ISS)
- Drug Abuse and Overdosage
- Integrated Summary of Benefits and Risks of the Drug

Section 10: Statistical Section:

- The subsections listed in the Clinical Data Section 8 are duplicated for Section 10.

Section 11: Case Report Tabulations (CRTs) - provided on CD-ROM in volume 39

- Data Listings are provided as CRTs. The Data Listings from the pivotal study is provided only electronically and are prepared as described in the FDA Guidance, "Providing Regulatory Submissions in Electronic Format-NDAs" (January 1999).
- SAS transport datasets for the pivotal study are also provided.
- Data listings (domain profile format) from other clinical studies are provided on paper only (as appendices to the individual study reports).

Section 12: Case Report Forms (CRFs) - provided on CD-ROM in volume 39

- CRFs for the patient population proposed in Section 3.8 dated August 30, 1999 (IND [redacted] Serial No. 218) are provided and organized as described in the FDA guidance of January 1999. These are provided electronically only.

The overall size of the electronic file contained in volume 39 is approximately The virus scanning software used for the submissions is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

Bioequivalence Study

On May 29, 1996 (IND [redacted] Serial 151) Novartis requested the use of a generic tamoxifen formulation (Tamofen[®] manufactured by Leiras Oy of Finland) to be used as the comparative agent in the large first-line and adjuvant international studies. In a subsequent FDA letter dated June 25, 1996, the use of this generic tamoxifen was deemed acceptable provided a bioequivalency study was conducted. The bioequivalence study report (Protocol 102) comparing Tamofen to the US approved formulation (Nolvadex) is now near completion. On May 16, 2000 (IND [redacted] Serial No. 232) Novartis requested permission to file this sNDA early without Study Report P102. We will submit this report within 30 days of the filing of this sNDA, which was agreed in a FDA fax dated June 28, 2000. The PK data for study P102 will also be provided electronically at that time.

Pediatric Waiver -

A request for a waiver from pediatric labeling for Femara in any indication involving the endocrine treatment of breast cancer was submitted to the IND [redacted] on June 6, 2000 (Serial No. 233). The basis for this waiver is that necessary pediatric studies would be impossible or highly impractical to conduct because of the small number of such patients.

90-Day Conference

We would like to request a 90-day post-submission conference as provided for by 21 CFR 314.102. We would like to have the opportunity to meet with you and be advised of the general status of your review of this application and to discuss the review classification and potential for an advisory committee hearing.

A certified copy of Section 3 of this NDA is being provided to our district office in compliance with the pre-approval inspection (PAI) requirements.

The FDA User Fee for this application (user fee ID 3694) was submitted on June 13, 2000.

Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent.

If you have any questions or comments regarding this sNDA, please contact me at (973) 781-2282.

Sincerely,



Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356H
Form FDA 3397
Volumes 1-39



Staten

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND [redacted]

JUL 7 2000

Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, NJ 07936-1080

Attention: Robert Miranda
Associate Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Reference is made to your correspondence dated June 6, 2000, requesting a waiver of pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Femara (letrozole tablets) for the treatment of breast cancer for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have any questions, please contact Ann Staten, Project Manager, at (301) 594-5770.

Sincerely yours.

[redacted signature]
/S/

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Orig. IND: [REDACTED]
Div. File
HFD-150/AStaten/MCohen/JJohnson/Pease
HFD-40/Temple/Behrman
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-6-KRoberts

R/D DPease/6-27-00
initiated by: MCohen 6-28-00
 JJohnson 6-30-00

F/T dwp/7-5-00

PEDIATRIC STUDY WAIVER

151
7-5-00

17 pages redacted from this section of
the approval package consisted of draft labeling