CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-726

CHEMISTRY REVIEW(S)

Division of Oncology Drug Products
Chemist's Memo

APR 22 1997

To: Eva Tolgyesi, HFD-150

From: Paul E. Dietze, HFD-150

Concerning: NDA 20-726 - Statistical Consult for Femara

Date: April 22, 1997

The statistical consult for Femara has been completed. Based on the statisticians findings I would recommend granting the requested two year expiration dating period (see attached statistical review). This recommendation is based on the conclusion of the statistician that the "findings do support an extrapolated expiration dating period of 24 months" (see conclusions of attached ststistical review), the supporting stability data provided in the NDA and the stability of the drug substance (see NDA reviews).

With respect to CMC issues the NDA can be approved pending an acceptable EER for the final manufacturing facility and pending a satisfactory Biopharm. consult.

4/22/97

Paul E. Dietze, Ph.D.
Review Chemist, HFD-150

I agree with Dr. P. Dietze's conclusion.

Eva Tolgyesi

4-22-97

cc: HFD-150 NDA 20-726
HFD-150 Division file
HFD-150/PDietze
HFD-150/LZhou
HFD-150/ETolgyesi
HFD-150/DSpillman

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MAR 12 1997

DIVISION OF ONCOLOGY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-726 **CHEM. REVIEW #:** 3 **REVIEW DATE:** March 12, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC Amendment	2-27-97	3-3-97	3-6-97
BC Amendment	3-27-97	3-28-97	4-2-97
BC Amendment	3-27-97	3-28-97	4-2-97

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals
59 Route 10
East Hanover, NJ 07936-1080
(formerly Ciba Pharmaceuticals Division,
Ciba-Geigy Corporation)

DRUG PRODUCT NAME

Proprietary:	Femara
Nonproprietary/USAN:	Letrozole
Code Name/#:	CGS 20267
Chem. Type/Ther. Class:	1S

ANDA Suitability Petition/DESI/Patent Status: USP 4,978,672 (exp. date 12/18/2007)
USP 5,352,795 (exp. date 10/4/2011)
USP 5,473,078 (exp. date 10/4/2011)

PHARMACOL. CATEGORY/INDICATION: advanced breast cancer in post menopausal women

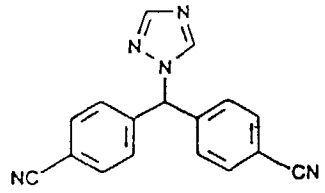
DOSAGE FORM:	Tablet
STRENGTHS:	2.5 mg
ROUTE OF ADMINISTRATION:	oral
DISPENSED:	X Rx _____ OTC

APP 2 6 1997

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

4,4'-[(1H-1,2,4-Triazol-1-yl)methylene] bis-benzonitrile (1)

M.W. = 285.31, Chemical Formula = $C_{17}H_{11}N_5$



SUPPORTING DOCUMENTS:

IND	Ciba-Geigy Corp	Femara Tablets
DMF		
DMF		

DMF

DMF

DMF

DMF

RELATED DOCUMENTS (if applicable): NA

CONSULTS:

EA	Approved	EA was submitted to HFD-102 for review on 8-22-96. The review was completed on 10-25-96. Minor deficiencies were noted and communicated to the to the applicant. The applicant has addressed the deficiencies and a FONSI was completed on 3-5-97 and is attached to this review.
Microbiology	Approved	Submitted to HFD-160 to evaluate the specifications for aerobic bacteria, yeast, mold and microorganisms. Submitted on 8-22-96. Review

		returned on 10-21-96. Deficiencies were be communicated to the applicant on 12-12-96. The deficiencies were addressed and a consult was forwarded to the reviewing microbiologist to evaluate the applicant's response. The microbiologist found the applicant's response satisfactory and recommended approval.
Biopharm.	Pending	Submitted to HFD-860 to evaluate the dissolution test method and the bioequivalence of the different formulations of the DP. Submitted on 8-22-96.
Pharm./Tox.	NA	Submitted to evaluate potential DEP and DBT levels in the DP on 8-22-96. However, the issue concerning DEP and DBT levels has been resolved.
Statistics	Pending	A consult was forwarded, on 3-10-97, to biostatistics in order to have the stability data evaluated

OTHER REQUESTS:

Trademark Review	Approved	Name found acceptable by the LNC on 11-8-96
EER	Pending	Submitted on 8-22-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS: This submission is a response to deficiencies communicated to the applicant by facsimile on January 27, 1997.

Drug Substance: With regards to the drug substance: the applicant has provided an adequate response to the single issue concerning the drug substance.

Drug product: With regards to the drug product: the applicant has addressed all deficiencies in a satisfactory manner.

CONCLUSIONS & RECOMMENDATIONS:

The applicant has adequately addressed all of the CMC deficiencies. Assuming there is no problem with the statistical consult, Biopharm consult or with the EER, NDA 20-726 can be approved with respect to CMC issues. As of April 9, 1997 all of the manufacturing facilities on the EER were acceptable except for the Ciba Geigy, Stein, facility which was pending an inspection.

However, the CSO should request that the applicant commit to when they will

name a supplier of NF grade iron oxide.

cc:
Orig. NDA 20-726
HFD-150/Division File
HFD-150/PDietze
HFD-150/LZhou
HFD-151/DSpillman
HFD-150/ETolgyesi

Liang Zhou 3/12/97

Liang Zhou, Ph.D.
Chemist Drug Substance

Paul E Dietze 3/12/97

Paul E. Dietze, Ph.D.
Chemist Drug Product

Approval is recommended pending favorable Biopharm Consult, Statistical Consult and CGMP compliance status of all manufacturing facilities.

Eva Tolgyesi

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

3/12/97

DIVISION OF ONCOLOGY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

JAN 2 4 199

NDA #: 20-726 CHEM. REVIEW #: 2 REVIEW DATE: January 16, 1997

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC	11-21-96	11-21-96	12-02-96
BZ	12-30-96	01-02-97	01-06-97
BC	01--8-97	01-10-97	01-14-97

NAME & ADDRESS OF APPLICANT: Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Ave.
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary:	Femara
Nonproprietary/USAN:	Letrozole
Code Name/#:	CGS 20267
Chem. Type/Ther. Class:	1S

ANDA Suitability Petition/DESI/Patent Status: USP 4,978,672 (exp. date 12/18/2007)
USP 5,352,795 (exp. date 10/4/2011)
USP 5,473,078 (exp. date 10/4/2011)

PHARMACOL. CATEGORY/INDICATION: advanced breast cancer in post menopausal women

DOSAGE FORM: Tablet
STRENGTHS: 2.5 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:
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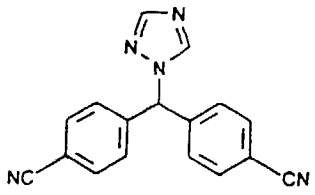

SUPPORTING DOCUMENTS:

IND	Ciba-Geigy Corp	Femara Tablets

DMF

DMF

DMF

DMF

DMF

DMF

RELATED DOCUMENTS (if applicable): NA

CONSULTS:

EA	Pending	EA was submitted to HFD-102 for review on 8-22-96. The review was completed on 10-25-96. Minor deficiencies were noted, these will be communicated to the applicant.
Microbiology	Pending	Submitted to HFD-160 to evaluate the specifications for aerobic bacteria, yeast, mold and microorganisms. Submitted on 8-22-96. Review returned on 10-21-96. Deficiencies were be communicated to the applicant on 12-12-96. The deficiencies were addressed in this

		submission. A consult was forwarded to the reviewing microbiologist to evaluate the applicant's response. The microbiologist found the applicant's response satisfactory and recommended approval. The microbiologist's review #2 is attached to the end of this review.
Biopharm.	Pending	Submitted to HFD-860 to evaluate the dissolution test method and the bioequivalence of the different formulations of the DP. Submitted on 8-22-96.
Pharm./Tox.	NA	Submitted to evaluate potential DEP and DBT levels in the DP on 8-22-96. However, the issue concerning DEP and DBT levels has been addressed in this review.
Statistics	Pending	

OTHER REQUESTS:

Trademark Review	Approved	Name found acceptable by the LNC on 11-8-96
EER	Pending	Submitted on 8-22-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS: These three submissions provide updated stability data for the drug product and address the deficiencies from our initial review of the NDA and communicated to the applicant by Agency letter dated 10-5-96.

Drug Substance: With regards to the drug substance the applicant has adequately addressed most of the deficiencies. There is, however, one minor deficiency that still needs to be addressed.

Drug product: With regards to the drug product the applicant has addressed most of the deficiencies. However, there are several issues that have not been addressed in a satisfactory manner. These issues need to be communicated to the applicant.

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-637 is not approvable with regards to chemistry manufacturing and controls issues. Several deficiencies still need to be addressed by the applicant.

cc:
Orig. NDA 20-726
HFD-150/Division File
HFD-150/PDietze
HFD-150/LZhou
HFD-151/DSpillman
HFD-150/ETolgyesi

11/16/97

Liang Zhou, Ph.D.
Chemist Drug Substance

11/16/97

Paul E. Dietze, Ph.D.
Chemist Drug Product

1/24/97

Eva Tolgyesi, Ph.D.
Chemistry Team Leader

OCT - 8 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-726 **CHEM. REVIEW #:** 1 **REVIEW DATE:** 9-30-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7-24-96	7-25-96	8-02-96

NAME & ADDRESS OF APPLICANT: Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Ave.
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary:	Femara
Nonproprietary/USAN:	Letrozole
Code Name/#:	CGS 20267
Chem. Type/Ther. Class:	1S

ANDA Suitability Petition/DESI/Patent Status: USP 4,978,672 (exp. date 12/18/2007)
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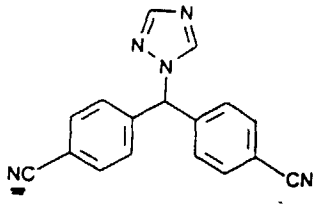

SUPPORTING DOCUMENTS:

IND	Ciba-Geigy Corp	Femara Tablets

DMF

DMF

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RELATED DOCUMENTS (if applicable): NA

CONSULTS:

EA	Pending	EA was submitted to HFD-102 for review on 8-22-96.
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Pharm./Tox.	Pending	Submitted to evaluate potential DEP

		and DBT levels in the DP. Submitted on 8-22-96.

OTHER REQUESTS:

Trademark Review	Pending	Submitted on 8-22-96.
EER	Pending	Submitted on 8-22-96.
Methods Validation	Pending	Will be initiated after all methods deficiencies have been addressed.

REMARKS/COMMENTS:

Drug Substance: There are several deficiencies relating to the drug substance. Most of the deficiencies are not serious and should be relatively simple for the applicant to address.

Drug product: There are numerous deficiencies concerning the drug product. Most of the deficiencies are not serious and should be relatively simple for the applicant to address. However, the stability data for the drug product is extremely limited. The lack of stability data is the most serious concern.

CONCLUSIONS & RECOMMENDATIONS:

The NDA is not approvable with respect to CMC issues. There are several deficiencies that need to be addressed. In addition, several consults and the EER are outstanding.

cc:
Orig. NDA 20-726
HFD-150/Division File
HFD-150/PDietze
HFD-150/LZhou
HFD-151/DSpillman
HFD-150/ETolgyesi

Liang Zhou 9/30/96

Liang Zhou, Ph.D.
Chemist Drug Substance

9/30/96

Paul E. Dietze, Ph.D.
Chemist Drug Product

10/2/96

Eva Tolgyesi, Ph.D.
Chemistry Team Leader