CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-428/S-001-S-007

Trade Name: AZELEX 20% CREAM

Generic Name:(azelaic acid)

Sponsor: Allergan Herbert Division of Allergan, Inc.

Approval Date: May 17, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 20-428/S-001-S-007

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)			X	
Statistical Review(s)			X	
Microbiology Review(s)			X	
Clinical Pharmacology Biopharmaceutics Review(s)			X	
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Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-428/S-001-S-007

APPROVAL LETTER

5

MAY 17 1996

NDA 20-428/S-001

Allergan Herbert Division of Allergan Inc.
Attention: Mr. Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92713-9534

Dear Mr. Buxbaum:

Please refer to your supplemental New Drug Application (NDA) dated November 10, 1995, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid), 20% Cream.

The supplemental application provides for post-approval commitment, regrading a supplement for content uniformity as a condition of our approval letter dated September 13, 1995.

We have completed our review of this supplemental application and it is approved effective as of the date of this letter.

This approval affects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

/S/ 5/16/96

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDC III
Division of Dermatologic and
Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/ProjMgr/Roy Blay
HFD-540/Pharm/Mainigi
HFD-540/MO/Vaughan
HFD-540/Chem/Rejali EMR 5/10/96
HFD-540/DeCamp

5.1

MAY - 8

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:20-428	CHEM.REVIEW #: 1	REVIEW DATE:	04-15-1996
SUBMISSION/TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
SUPPLEMENT/SCS-001	11-10-1995	11-13-1995	11-17-1995

NAME & ADDRESS OF APPLICANT:

Allergan Herbert
Division of Allergan Inc.
2525 Dupont drive
P.O. Box 19534
Irvine, CA 92713-9534

DRUG PRODUCT NAME

Proprietary: AZELEX (azelaic acid) 20% Cream
Nonproprietary/USAN: Azelaic acid) 20% Cream

Code Names/#'s:
Chemical Type/
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: X Rx _____ OTC

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

1,7-heptanedicarboxylic acid, or
1,9-nonanedioic acid, or
lepargylic acid, or
anchoic acid

$HOOC(CH_2)_7COOH$ Mol. weight: 188.23
$C_9H_{16}O_4$ CAS# 123-99-9

SUPPORTING DOCUMENTS:

Dated: August 10, 1995, commitments with respect to CMC deficencies
Recevied:August 18, 1995.

REMARKS/COMMENTS:

This supplement provides for post-approval commitment, regrading a supplement for content uniformity as a condition of our approval letter dated September 13, 1995. The applicant has implemented the content uniformity testing for both azelaic acid and benzoic acid as part of the long term stability program. The content uniformity test is conducted by using on a reversed-phase column. The method is the same as was provided in the original application.

The samples are taken from two tubes which is cut along their length. The specimen are taken from the centers of the upper, middle and lower portions of each tubes. Duplicate injections is performed on six sample solutions, making a total of 12 determinations. The specification is as follows:

- Mean of all 12 data points falls within % of label claim for azelaic acid, and % of label claim for benzoic acid.
- All of 12 injections fall within % of label claim for azelaic acid , and % of label claim for benzoic acid.
- Means will also be reported separately for each of the top, middle, and bottom replicate determinations.

The revised stability protocol addresses the content uniformity including sampling is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval letter to issue for this supplement.

/ST

Nahid Mokhtari-Rejali, Ph. D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/ProjMan/Roy Blad
HFD-540/Pharm/Mainigi
HFD-540/MedOffr/Vaughn
HFD-540/Chem/NM Rejali/5/7/96
HFD-540/WHDecamp

concur 5/10/96
WHD 5/8/96

filename: C:\nda\nda20-428.001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date NOV 16 1995

NDA No. 20-428

Allergan Herbert Division of Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Attention: Stephen Buxbaum
Director
Worldwide Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: AZELEX (azelaic acid cream) 20%

NDA Number: 20-428

Supplement Number: S-001 and S-002

Date of Supplement: November 10, 1995

Date of Receipt: November 13, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

/S/

for Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products Topical
Center for Drug Evaluation and Research

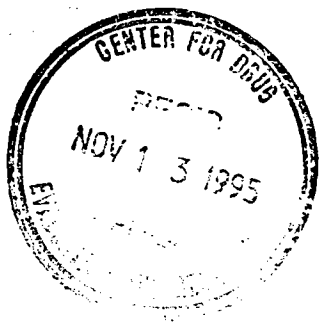
ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

20428

SCS controls

November 10, 1995



Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Ophthalmic Drug Products (HFD-540)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: AZELEX™ (azelaic acid cream) 20%
NDA 20-428
Post-Approval Commitment: Content Uniformity Testing

Dear Doctor Wilkin,

On September 13, 1995, FDA approved AZELEX™ (azelaic acid cream) 20% as a prescription pharmaceutical. The September 13 approval letter stipulated the following as a condition of the approval, which Allergan herein satisfies:

> Within 60 days of approval, a supplement will be submitted that amends the content uniformity protocol.

Allergan hereby implements Content Uniformity testing of both azelaic acid and benzoic acid as part of the long term stability program. Results will be reported to FDA as part of the program. which is provided in describes the collection of data to be used in the testing. These data consist of twelve (12) data points for each of azelaic acid and benzoic acid. The specification is as follows:

- *Mean* of **ALL 12** data points falls within % of label claim for azelaic acid, and % of label claim for benzoic acid.
- **ALL 12** injections fall within % of label claim for azelaic acid, and % of label claim for benzoic acid.
- Means will also be reported separately for each of the top, middle and bottom replicate determinations.

I trust that the information herein provided satisfies the relevant post-approval commitment.

Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

5.1

MAY 17 1996

NDA 20-428/S-002

Allergan Herbert Division of Allergan Inc.
Attention: Mr. Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92713-9534

Dear Mr. Buxbaum:

Please refer to your supplemental New Drug Application (NDA) dated November 10, 1995, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid), 20% Cream.

The supplemental application provides for a particle size and/or agglomeration specification for azelaic acid as a condition of our approval letter dated September 13, 1995.

We have completed our review of this supplemental application and it is approved effective as of the date of this letter.

This approval affects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

/S/ 5/16/96

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDC III
Division of Dermatologic and
Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/ProjMgr/Roy Blay
HFD-540/Pharm/Mainigi
HFD-540/MO/Vaughan
HFD-540/Chem/Rejali MMR 5/10/96
HFD-540/DeCamp

5.1

MAY -8 1996

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:20-428	CHEM.REVIEW #: 1	REVIEW DATE: 04-22-1996

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT/SCS-002	11-10-1995	11-13-1995	11-17-1995

NAME & ADDRESS OF APPLICANT:

Allergan Herbert
Division of Allergan Inc.
2525 Dupont drive
P.O. Box 19534
Irvine, CA 92713-9534

DRUG PRODUCT NAME

Proprietary: AZELEX (azelaic acid) 20% Cream
Nonproprietary/USAN: Azelaic acid) 20% Cream

Code Names/#'s:
Chemical Type/
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

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

1,7-heptanedicarboxylic acid, or
1,9-nonanedioic acid, or
lepargylic acid, or
anchoic acid

$HOOC(CH_2)_7COOH$ Mol. weight: 188.23
$C_9H_{16}O_4$ CAS# 123-99-9

SUPPORTING DOCUMENTS:

Dated: August 18, 1995, Commitments with respect to CMC deficiencies
Received:August 18, 1995.

REMARKS/COMMENTS:
This supplement provides a particle size and/or agglomeration specification for azelaic acid as a condition of our approval letter dated September 13, 1995. Base on our request the applicant has revised the drug product specification for particle size as "a particle size maximum of μm for any single crystal, with no agglomerate particles μm."

However, the existing product shelf life specification for microscopy remains the same, μm for single crystals as proposed in the original submission. The release specification is as follows:

Specifications for AZELEX™ (azelaic acid) 20% cream.
The finished product is tested in accordance with and to the attached release and product (shelf-life) methods and specifications.

Test Parameter	Release Specifications	Product Specifications	Test Method
Physical Appearance:	White, opaque cream	White, opaque cream	
ID test for Azelaic Acid:	Meets Test Requirement	-----	
ID test for Benzoic Acid:	Meets Test Requirement	-----	
Content of Azelaic Acid:	g % of label)	g % of label)	
Content of Benzoic Acid:	g % of label)	g % of label)	
Microbial Contamination: (Microbial Limit Test)	Passes BP	Passes BP	
Filled Weight: 30 g tube:	mean fill g per tube; individual filled weight g per tube.	-----	
5 g tube:	mean fill g per tube; individual filled weight g per tube		
Microscopy:	Individual crystals μm; Agglomerate particles μm	Individual crystals ≤ 75μm	
Micropenetration:	-----	mm	
Microbial Challenge Test: (Preservative Effectiveness)	-----	Passes USP, BP	

* Testing Standard ‡ Quality Specification (1) Release method (2) Shelf-life method

The finished product is tested in accordance with and to the attached release product method and specification. In addition to the revised particle size specification, testing standard, quality standards, and removal of decomposition product testing have been updated. As we suggested, the stability data of the first three batches indicates the absence of decomposition of azelaic acid. Therefore, this test has been deleted.

The revised specification meets our proposed particle size specification for azelaic acid and is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval letter to issue for this supplement.

/S/

Nahid Mokhtari-Rejali, Ph. D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/ProjMan/Roy Blay
HFD-540/Pharm/Mainigi
HFD-540/MedOffr/Vaughn
HFD-540/Chem/NM Rejali/5/7/96
HFD-540/WHDecamp

5/10/96
5/9/96

filename: c:\nda\nda20-428

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date NOV 16 1995

NDA No. 20-428

Allergan Herbert Division of Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534
Attention: Stephen Bunbaum
Director
Worldwide Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: AZELEX (azelaic acid cream) 20%

NDA Number: 20-428

Supplement Number: S-001 and S-002

Date of Supplement: November 10, 1995

Date of Receipt: November 13, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

/S/

for Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products Topical
Center for Drug Evaluation and Research

FORM FDA 3217d (12/91)

701

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

November 10, 1995

Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Ophthalmic Drug Products (HFD-540)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: AZELEX™ (azelaic acid cream) 20%
NDA 20-428
Post-Approval Commitment: Microscopy Release Specification

Dear Doctor Wilkin,

On September 13, 1995, FDA approved AZELEX™ (azelaic acid cream) 20% as a prescription pharmaceutical. The September 13 approval letter stipulated the following as a condition of the approval, which Allergan herein satisfies:

> Within 60 days of approval, a supplement will be submitted that establishes a particle size and/or agglomeration specification for azelaic acid.

In the undated chemistry deficiencies document received via facsimile on August 8, 1995, under Point 1, FDA states that Allergan should implement the following as a *release* specification: "For microscopy, a particle size maximum of µm for any single crystal, with no agglomerate particles µm." Allergan hereby establishes the specification as requested. The existing *product (shelf life)* specification for microscopy, which is performed and reported to FDA as part of the long term stability program, is µm for single crystals. Documentation supporting or related to the new release specification is attached as listed below. The documentation has been revised as appropriate to incorporate the new specification.

Attachment No.	Document No./Date	Description
1	NDA 20-428, Section 3.II.F. (revised)/ Nov. 10, 1995	Specifications and Analytical Procedures for the Drug Product
2	QS[1] No. KV02EG30/ Sept. 26, 1995	Finished product release specification for AZELEX™ cream
3	TS[2] No. K295E920/ Sept. 22, 1995	Testing Standard for stability testing of AZELEX™ cream

1. Quality Specification; 2. Testing Standard

The original version of the Attachment 1 document appears on p. 5 001 of the NDA. In addition to adding the new specification, the document has been revised to reflect a) updated Testing Standards, b) updated Quality Standards, and c) removal of Decomposition Products testing in accordance with CMC Question 3 of the March 9, 1995, response to the NDA not approvable letter of February 28, 1995. Minor editorial revisions have also been made.

I trust that the documentation herein provided satisfies the relevant post-approval commitment.

Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

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MAY 17 1996

NDA 20-428/S-003

Allergan Herbert Division of Allergan Inc.
Attention: Mr. Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92713-9534

Dear Mr. Buxbaum:

Please refer to your supplemental New Drug Application (NDA) dated November 10, 1995, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid), 20% Cream.

The supplemental application provides for an x-ray powder diffraction method and specification for polymorphs A (α) and B (β) of azelaic acid as a condition of our approval letter dated September 13, 1995.

We have completed our review of this supplemental application and it is approved effective as of the date of this letter.

This approval affects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

/S/ 5/16/96

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDC III
Division of Dermatologic and
Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/ProjMgr/Roy Blay
HFD-540/Pharm/Mainigi
HFD-540/MO/Vaughan
HFD-540/Chem/Rejali HMR 5/10/96
HFD-540/DeCamp

5.

MAY 10 1996

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #:20-428	CHEM.REVIEW #: 1	REVIEW DATE: 04-22-1996

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT/SCS-003	11-10-1995	11-13-1995	11-17-1995

NAME & ADDRESS OF APPLICANT:

Allergan Herbert
Division of Allergan Inc.
2525 Dupont drive
P.O. Box 19534
Irvine, CA 92713-9534

DRUG PRODUCT NAME

Proprietary: AZELEX (azelaic acid) 20% Cream
Nonproprietary/USAN: Azelaic acid) 20% Cream

Code Names/#'s:
Chemical Type/
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: __X__ Rx _____ OTC

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

1,7-heptanedicarboxylic acid, or
1,9-nonanedioic acid, or
lepargylic acid, or
anchoic acid

$HOOC(CH_2)_7COOH$ Mol. weight: 188.23
$C_9H_{16}O_4$ CAS# 123-99-9

SUPPORTING DOCUMENTS:

Dated: August 10, 1995, Commitments with respect to CMC deficiencies
Received: August 18, 1995.

REMARKS/COMMENTS:
This supplement provides an X-ray powder diffraction method and specification for polymorphs A (α) and B (β) of azelaic acid as a condition of our approval letter dated September 13, 1995, Based on our recommendation, Allergan, in conjunction with the contract manufacturer of azelaic acid have established an upper limit on polymorph B.

The appliacnt has established a specification of % for polymorph B in the azelaic acid drug substance.

Azelaic Acid Drug Substance Specification

Appearance:	white crystalline powder
Infrared absorption spectrum:	The spectrum of the sample substance shall only exhibit maxima at the same wave numbers and with the same relative intensities as those of the reference spectrum.
Melting range:	105 to 110 °C
Acetone:	not more than %
Clarity of solution:	clear
Color of solution:	not more intense than reference solution
Heavy metals:	color not more intense than reference solution, corresponding to not more than %
Sulfated ash:	not more than %
Related substances:	heptanedioic acid not more than %, decanedioic acid not more than %, undecanedioic acid not more than %, dodecanedioic acid not more than %, each additional less than % total not more than %
Water content:	not more than %
Assay:	%, calculated on the anhydrous and solvent-free basis
Addendum for Micro grade	
Particle size:	no particle larger than µm, not more than particles in a range of not less than µm to not more than µm
Polymorphism	form α does not contain more than % form β
Tests	
Conduct the tests as per	issued 01 Sep. 95.

The specification for azelaic acid under "Polymorphism" states:"form α does not contain more than % form β."

Azelaic acid exists in two solid state forms, called modification α and β. Since azelaic acid in its main form modification α may contain small amount of modification β, the two modification is discriminated from each other by X-ray powder diffraction. The limit of detection of modification β in mixtures of both modifications is estimated by X-ray powder diffraction (XRPD). The testing standard for the X-ray diffraction test method (XRPD)is provided as follows:

Polymorphism (x-ray powder diffraction method, XRPD)

Test

Test conditions

Apparatus:	**transmission diffractometer**
Beam:	**germanium monochromatized radiation**
Detector:	**linear position-sensitive proportional counter**
Technique:	**transmission**
Test range:	
Step range:	
Test duration:	

The data from three batches (34058564, 15058743 & 25058894) of azelaic acid as well as their diffractograms are provided, The data indicate when β is present in amounts equal or greater than %, the additional reflection at is observed. Amount smaller than this, like % of Polymorph B in Polymorph A, cannot be clearly identified in each sample. In the X-ray pattern of mixtures with amounts of polymorph B equal or greater than % other additional reflections corresponding to polymorph B are detectable. Because of the dependence of the absolute intensities from the particle size distribution it is not possible to give an intensity value of the reflection of for the different levels of modification β in the mixture. However, the ratio of the relative intensities of this reflection of modification of and of neighboring reflection of in all sample investigated with amounts of modification β equal or less than % smaller than Therefore, the limit of detection of Polymorph B in mixtures of both modifications was established to be % relative to polymorph A.

The revised specification meets our proposed particle size specification for azelaic acid and is acceptable. has also amended their DMF by adding the new specification on polymorph B

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval letter to issue for this supplement.

/S/

Nahid Mokhtari-Rejali, Ph. D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/ProjMan/Roy Blay
HFD-540/Pharm/Mainigi
HFD-540/MedOffr/Vaughn 5/10/96
HFD-540/Chem/NM Rejali/6/7/96
HFD-540/WHDecamp NLT 10/96

filename: C:\nda\nda20-428.003

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date NOV 29 1995

NDA No. 20-428

Allergan Herbert Division of Allergan Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534
Attention: Stephen Burbaum

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Azelex cream 20%

NDA Number: 20-428

Supplement Number: S-003

Date of Supplement: November 10, 1995

Date of Receipt: November 13, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

/S/

for Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products Topical
Center for Drug Evaluation and Research

6.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-004

NOV 27 1996

Allergan Herbert Division of Allergan Inc.
Attention: Mr. Stephen Buxbaum
Director, Worldwide Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92713-9534

Dear Mr. Buxbaum:

Please refer to your July 17, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid) 20% Cream.

The supplemental application provides for a correlation between viscosity and penetration for azelaic acid as a condition for post-approval commitments of our approvable letter dated September 13, 1995.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Olga Cintron, R.Ph.
Consumer Safety Officer
(301) 827-2020

Sincerely yours,

/S/ 11/27/96

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDC III
Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

Original NDA 20-428
HFD-540/Div. Files
HFD-540/CSO/OCintron
HFD-540/Chem/NMRejali NMR 11/25/96
HFD-540/MO/Vaughan
HFD-540/Pharm/Mainigi
HFD-160/Micro/King
HFD-540/TLChem/WHDeCamp
HFD-830/E.Sheinin
HFD-80
DISTRICT OFFICE
HFD-232
HFD-354/YanaMille

APPROVAL

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 **CHEM. REVIEW #**: 1 **REVIEW DATE**: 17-OCT-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT/SCS-004	17-JUL-1996	19-JUL-1996	24-JUL-1996

NAME & ADDRESS OF APPLICANT: Allergan Herbert Division of Allergan Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

DRUG PRODUCT NAME

Proprietary:	AZELEX (azelaic acid) 20% Cream
Nonproprietary/USAN:	Azelaic acid 20% cream
Code Names/#'s:	AGN 191861
Chemical Type/ Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Topical treatment of acne vulgaris

DOSAGE FORM:	Cream
STRENGTHS:	20%
ROUTE OF ADMINISTRATION:	Topical application
DISPENSED:	__X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1,7-heptanedicarboxylic acid, or
1,9-nonanedioic acid, or
lepargylic acid, or
anchoic acid

$HOOC(CH_2)_7COOH$ Mol. weight: 188.23
$C_9H_{16}O_4$ CAS# 123-99-9

PATENT STATUS:

4,292,326; for the treatment of hyperpigmentary dermatoses
4,386,104; for the treatment of acne
4,818,768; for the treatment of hyperpigmentary dermatoses including malignant melanoma.

Allergan is requesting an exclusivity period of five (5) years. However, the expiration dates of the patents are not included.

REMARKS/COMMENTS:

This supplement provides a correlation between viscosity and penetration for azelaic acid as a condition for post-approval commitments of our approvable letter dated September 13, 1995. The product micropenetration specification in orginal NDA was reported to be mm. *Allergan was required to "collect and submit data to establish a correlation between viscosity and penetration."*

The applicant has identified a suitable reference standard and normalizing data using the "Yield Value" equation. Furthermore, the micro penetration of

Azelex cream was obtained, and a certified viscosity standard was selected as a reference material during penetration testing. A log plot of the viscosity versus micropentration for viscosity standard ranging from centipoise was fit to a power indicating curve model. The square of the regression for the Power curve fit was found to be indicating a strong correlation between viscosity and micro penetration. In addition, these viscosity Standards have been included in the micro penetration method. For detailed information . Furthermore, this supplement contains an MSDS for the AZELEX finished product & the final stability protocol with approval signatures The applicant has also provided the page 9 of which was omitted from the original document, pp.05 007-024. In addition, the document has been corrected for an error which appeared on page 4, % (w/w)" has been replaced by %(w/w)" under

The applicant has also revised the micro penetration method presented in the original NDA.

The collected data for the three lots of Azelex cream satisfy the correlation between viscosity and penetration as was requested. It should be noted that the revised micro penetration method is in accordance with the above correlation study.

CONCLUSIONS/RECOMMENDATION:

Recommend approval letter to issued for this supplement. Applicant should be advised to use the agency supplement number after receiving the acknowledgment letter for future correspondence.

/ST

N. Mokhtari-Rejali, Ph.D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/DivFile
HFD-830/SupChem/Eric Sheinin
HFD-540/Chem/NMRejali/11/4/96
HFD-540/MO/Vaughan
HFD-540/Pharm/Mainigi
HFD-160/Micro/King
HFD-540/ProjMgr/Cintron
HFD-540/TLChem/WHDeCamp/ R/D Init by: WH 11/20/96

filename: **N20428.004**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUL 1 1996

NDA No. 20-428

Allergan Inc.
2525 Dupont Drive
P.O.Box 19534
Irvine,CA. 92713-9534

Attention: Stephen Burbaum
Director
Worldwide Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: AZELEX(azelaic acid cream)20%

NDA Number: 20-428

Supplement Number: SCS-004

Date of Supplement: June 17,1996

Date of Receipt: June 19,1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the

Act on August 18,1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Dermatologic and Ophthalmologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-540
Rockville, MD 20857

Sincerely yours,

/S/

For/ Chief, Project Management Staff
Division of Dermatologic and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

FORM FDA 3217j (11/95)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-005

JUN 29 1997

Allergan, Inc.
Attention: Mr. Stephen Buxbaum
Director, Worldwide Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92623-9534

Dear Mr. Buxbaum:

Please refer to your supplemental new drug application dated March 18, 1997, received March 21, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex™ (azelaic acid cream), 20%.

The User Fee goal date for this application is September 21, 1997.

The supplemental application provides for a change in the azelaic acid micronization plant from

We have completed the review of this supplemental application and it is approved, effective as of the date of this letter.

This approval affects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Olga Cintron, R.Ph., Project Manager, at (301) 827-2020.

Sincerely yours,

/S/ 6/24/97

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDCIII
Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

Original NDA 20-428
HFD-540/Div. Files
HFD-540/CSO/OCintron
HFD-540/Chem/WCTimmer WCT
HFD-540/ChemTmLdr/DeCamp
HFD-354/Yana Mille
HFD-830/DNDCIII Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

APPROVAL (AP)

DF

JUN 27 1997

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 09-MAY-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCM-005	18-MAR-97	21-MAR-97	09-MAR-97

NAME & ADDRESS OF APPLICANT:

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, C 92623-9534

Stephen Buxbuam
Director
Worldwide Regulatory Affairs
(714) 246-4534

DRUG PRODUCT NAME

Proprietary:	AZELEX™ (azelaic acid cream) 20%
Nonproprietary/USAN:	azelaic acid cream 20%
Code Names/#'s:	AGN191861
Chemical Type/ Therapeutic Class:	1 S

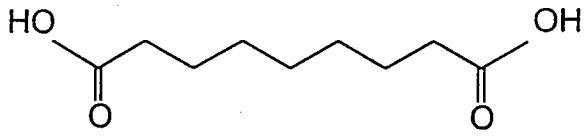
ANDA Suitability Petition/DESI/Patent Status:

PHARMACOLOGICAL INDICATION: Acne Vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ R_x _____ OTC

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

NAME:	Azelaic Acid
CHEMICAL NAME:	Nonanedioic Acid
SYNONYMS:	Lepargylic Acid, Anchoic Acid
CAS NUMBER:	123-99-9
MOLECULAR WEIGHT:	182.22
CHEMICAL FORMULA:	$C_9H_{16}O_4$
STRUCTURAL FORMULA:	$HO_2C(CH_2)_7CO_2H$



SUPPORTING DOCUMENTS:

NDA 20-428 AZELEX (azelaic acid) cream, 20%
DMF
DMF

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS:

See attached review of DMF dated 01-MAY-97.

This supplement was submitted for a change in the micronization site for azelaic acid from the

There is no change in the micronization procedure, equipment (identical in both plants), or sampling of the azelaic acid. Batch uniformity between the plant are essentially identical.

An EIR was found acceptable on 15-APR-97

CONCLUSIONS & RECOMMENDATIONS:

The supplement application is approvable for manufacturing and controls under section 505 of the FFD&C Act. All manufacturing facilities are currently in acceptable GMP compliance.

/S/

William C. Timmer, Ph.D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/Chem/WCTimmer
HFD-540/TmLdr/WHDeCamp
HFD-540/CSO/OCintron

6/17/97

filename: c:\wpwin61\wpdocs\cder\supplmnt\nda20428.sc

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-005

APR 9 1997

Allergan Herbert Division of Allergan Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Attention: Stephen Buxbaum
Director, Worldwide Regulatory Affairs

Dear Mr. Buxbaum:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: AZELEX (azelaic acid cream) 20%

NDA Number: 20-428

Supplement Number: S-005

Date of Supplement: March 18, 1997

Date of Receipt: March 21, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 20, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Mary J. Kozma-Fornaro
Acting Supervisor, Project Management Staff
Division of Anti-Infective Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

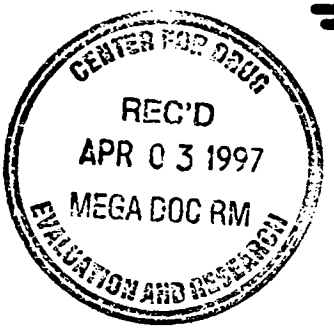
cc:
Original NDA 20-428/S-005
HFD-540/Div. Files
HFD-540/CSO/O. Cintron

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



April 1, 1997

S-005
SUPPL NEW CORRESP

Jonathan K. Wilkin, M.D.
Director, Division of Dermatologic & Dental Drug Products (HFD-540)
Central Document Room
Food and Drug Administration
9201 Corporate Boulevard, Building 2
Rockville, MD 20850

REF: AZELEX® (azelaic acid cream) 20%
NDA 20-428, SCM #005

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

Dear Doctor Wilkin:

Allergan Herbert, Skin Care Division of Allergan, Inc., requests that the enclosed "User Fee Cover Sheet" kindly be attached to the "Special Supplement - Changes Being Effected" submitted to the Agency on March 18, 1997, for the above referenced NDA. This form was inadvertently omitted in the original submission.

Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

Enclosure

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-006

SEP 4 1998

Allergan, Inc.
Attention: Stephen Buxbuam
Director
2525 Dupont Drive
P.O. box 19534
Irvine, Ca. 92623

Dear Mr. Buxbuam:

Please refer to your supplemental new drug application dated April 28, 1998, received April 30, 1998, submitted pursuant to section 505(b)of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid) Cream, 20%.

The user fee goal date for this application is October 29, 1998.

This supplemental new drug application provides for a 50 gram tube size with an eigthteen month (18) month expiration dating.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Olga Cintron, Project Manager, at (301) 827-2020.

Sincerely yours,

/S/ - 9/4/98

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for the
Division of Dermatologic and Dental
Drug Products, (HFD-540)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-428
HFD-540/Div. Files
HFD-540/O.Cintron
HFD-540/Vaughan
HFD-540/Mainigi
HFD-540/Timmer
HFD-540/DeCamp
HFD-95/DDMS (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE
filename: 20428II.WPD

APPROVAL (AP)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-006

1998

Allergan, Inc.
Attention: Mr. Stephen Buxbaum
Director, Worldwide Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Dear Mr. Buxbaum:

Please refer to your supplemental new drug application dated August 5, 1997, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Azelex (azelaic acid) cream 20%.

The User Fee goal date for this application is February 6, 1998.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(b) of the Act and 21 CFR 314.125 (b).

The specification based on USP <905>, "Uniformity of Dosage Units: Content Uniformity-Transdermal System, Inhalations, and Molded Tablets" is inappropriate for semi-solids such as creams. In addition, the stability data suggest that package integrity may be a problem during storage; however, a comprehensive failure analysis was not performed.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any question, please contact Mary Jean Kozma-Fornaro, R.N., M.S.A., Supervisory Consumer Safety Officer at (301) 827-2020.

Sincerely yours,

/S/ 1/23/98

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDCIII
Division of Dermatologic and Dental
Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: **Original NDA 20-428**
HFD-540/Div. Files
HFD-540/SCSO/MJKozma-Fornaro
HFD-540/MedOfcr/Vaughan
HFD-540/Pharm/Mainigi
HFD-540/Chem/Timmer 1/23/98
HFD-540/ChemTmLdr/DeCamp
HFD-344/Yana Mille
HFD-830/DNDCIII Division Director
HFD-92/DDM-DIAB
DISTRICT OFFICE

NOT APPROVABLE (NA)

AUG 26 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 **CHEM.REVIEW #**: 2 **REVIEW DATE**: 02-AUG-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCS-006	05-AUG-97	06-AUG-97	02-JAN-98
SCS-006/BC	28-AUG-97	29-AUG-97	02-JAN-98
SCS-006/AC	28-APR-98	30-APR-98	30-APR-98

NAME & ADDRESS OF APPLICANT: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, C 92623-9534

Stephen Buxbuam
Director
Worldwide Regulatory Affairs
714-246-4534

DRUG PRODUCT NAME

Proprietary: AZELEX™ (azelaic acid cream) 20%
Nonproprietary/USAN: azelaic acid cream 20%
Code Names/#'s: AGN191861
Chem. Type/Class: 1 S

PHARMACOLOGICAL INDICATION: Acne Vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ R_x _____ **OTC**

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

NAME: Azelaic Acid
CHEMICAL NAME: Nonanedioic Acid
SYNONYMS: Lepargylic Acid, Anchoic Acid
CAS NUMBER: 123-99-9
MOLECULAR WEIGHT: 182.22
CHEMICAL FORMULA: $C_9H_{16}O_4$
STRUCTURAL FORMULA: $HO_2C(CH_2)_7CO_2H$

SUPPORTING DOCUMENTS: None

REMARKS/COMMENTS:

This supplement was submitted in response to the NOT APPROVABLE letter issued 6 January 1998 for supplement NDA 20-428/SCS-006, which proposed the addition of a 50 gram tube size.

In this submission the sponsor has submitted stability data for the 50 gm tube size in excess of 12 months. These data were obtained via the specifications approved in the NDA and supplement SCS-007. All data from three lots of 50 gm tubes, with the exception of one assay point at 6 months, were within product specifications. This outlier was throughly investigated and no rational explanation could be found or proposed. Accelerated stability data for six months was also submitted.

Accordingly, an eighteen month (18) month shelf-life (or expiry period) is approved for azelaic acid in 50 gm tubes.

Submission of continuously obtained stability data may warrant an extension of the expiry period.

CONCLUSIONS & RECOMMENDATIONS:

The supplement application is APPROVABLE for manufacturing and controls under section 505 of the FFD&C Act.

/S/

William C. Timmer, Ph.D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/Chem/WCTimmer
HFD-540/TmLdr/WHDeCamp WD 8/26/98
HFD-540/CSO/OCintron

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8.1

JAN 19 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 **CHEM.REVIEW #**: 1 **REVIEW DATE**: 02-JAN-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCS-006	05-AUG-97	06-AUG-97	02-JAN-98
SCS-006/BC	28-AUG-97	29-AUG-97	02 JAN-98

NAME & ADDRESS OF APPLICANT: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, C 92623-9534

Stephen Buxbuam
Director
Worldwide Regulatory Affairs
(714) 246-4534

DRUG PRODUCT NAME

Proprietary:	AZELEX™ (azelaic acid cream) 20%
Nonproprietary/USAN:	azelaic acid cream 20%
Code Names/#'s:	AGN191861
Chemical Type/ Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOLOGICAL INDICATION: Acne Vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ R_x _____ OTC

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

NAME: Azelaic Acid
CHEMICAL NAME: Nonanedioic Acid
SYNONYMS: Lepargylic Acid, Anchoic Acid
CAS NUMBER: 123-99-9
MOLECULAR WEIGHT: 182.22
CHEMICAL FORMULA: $C_9H_{16}O_4$
STRUCTURAL FORMULA: $HO_2C(CH_2)_7CO_2H$

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS:

This supplement was submitted to support the following changes:

1. a new packaging size: 50 grams,

2. a modified content uniformity method, and

3. a new micropenetration specification.

The sponsor, Allergan, proposes to market a 50 gram size tube for azelaic acid, 20%. AZELEX® (azelaic acid cream) 20% is currently marketed in 5 and 30 g sizes.

Three batches of the drug product were manufactured and filled into 50 g tubes. The lots were then placed on stability. Both long-term % RH) and accelerated % RH) conditions were monitored for three months and six months, respectively. After six months of storage at % RH (long-term conditions), the lots were out of specification in azelaic acid content uniformity and micropenetration.

The sponsor proposed a new specification based on USP <905>, "Uniformity of Dosage Units: Content Uniformity-Transdermal Systems, Inhalations, and Molded Tablets."

USP <905> specification are inappropriate for semi-solids such as creams. In addition, the sponsor has not submitted a failure report; a reason for the failing specification is necessary. (As a starting point, the sponsor should consider packaging failure).

Therefore, this supplement is recommended as not approvable.

CONCLUSIONS & RECOMMENDATIONS:

The supplement application is NOT APPROVABLE for manufacturing and controls under section 505 of the FFD&C Act.

/S/

William C. Timmer, Ph.D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/Chem/WCTimmer
HFD-540/TmLdr/WHDeCamp
HFD-540/CSO/OCintron

WCT 1/14/97

filename: c:\wpwin61\wpdocs\cder\supplmnt\n20428-c.006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-006

Allergan, Inc.
2525 Dupont Drive, P.O. Box 19534
Irivine, CA 92623-9534

AUG 13 1997

Attention: Stephen Buxbaum
Director, Worldwide Regulatory Affairs

Dear Mr. Buxbaum:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Azelex® (azelaic acid cream) 20%

NDA Number: 20-428

Supplement Number: S-006

Date of Supplement: August 5, 1997

Date of Receipt: August 6, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 5, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-428/S-006
HFD-540/Div. Files
HFD-540/CSO/Olga Cintron

SUPPLEMENT ACKNOWLEDGEMENT

ALLERGAN

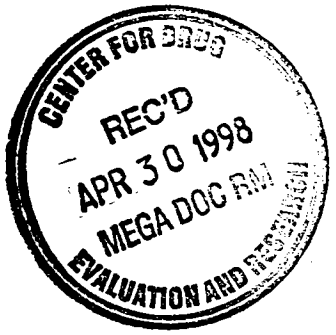
ORIGINAL

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

April 28, 1998

NDA SUPPL AMEND
SCS-006
(BC) AC per ESO

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: AZELEX® (azelaic acid cream) 20%
NDA 20-428 [S-006]
Deficiency Letter of January 6, 1998

Dear Dr. Wilkin:

Reference is made to your letter of January 6, 1998, regarding our supplemental application (S-006) for the addition of a 50 gram tube size.

A response to the letter for the above-referenced NDA is provided below. The deficiency issues are repeated in bold, italicized text.

The specification based on USP <905>, "Uniformity of Dosage Units: Content Uniformity-Transdermal System, Inhalations, and Molded Tablets" is inappropriate for semi-solids such as creams. In addition, the stability data suggest that package integrity may be a problem during storage; however, a comprehensive failure analysis was not performed.

Allergan accepts the Agency's contention that specifications based on the USP <905> monograph are not appropriate for a semi-solid dosage form, such as a cream. As a result, all stability study and out-of-specification (OOS) investigations described below were performed or evaluated based on the specifications approved in the NDA, including supplement S-007 approved September 27, 1997 (which expanded the shelf-life specification for azelaic acid content to %). We thus request that the proposal contained in this original submission (dated August 5, 1997 and amendment dated August 28, 1997) to amend the content uniformity specification, be considered withdrawn at this time.

ORIGINAL

Stability data in excess of 12 months is now available for the 50 g tube and is included in this response. All data from the three lots of 50 g tubes, with the exception of one assay point for batch 98C02-25°C at 6 months, are within product specifications through the study period. Our OOS investigation focused on three parameters. To account for the possibility of operator error, we had two analysts retest some of the samples to confirm the results. Within-specification results were obtained, so this did not account for the one discrepant result. We also examined the analytical methodology to assure that it was being followed and performed properly; this was the case. Manufacturing batch and filling records were examined for deviations; none were found. Thus, although an explanation for the one OOS result was not immediately forthcoming, nevertheless the data as a whole, which now includes test points up to 14 months, satisfied us that the content uniformity results are within specification, and that the single outlier result at 6 months was anomalous. In addition, visual inspection of the tubes revealed no package integrity problems.

Attached is a technical memorandum, which includes stability data, graphs and results of this investigation in detail. (Attachment 1)

We trust the information provided will be satisfactory for approval of this supplement for AZELEX® (azelaic acid cream) 20%, NDA 20-428.

Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

ALLERGAN

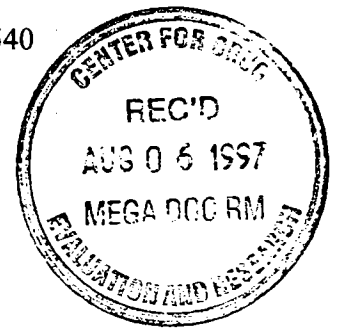
2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

ORIGINAL

August 5, 1997

NDA NO. 20428 REF NO 000
NDA SUPPL FOR 000

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: AZELEX® (azelaic acid cream) 20%
NDA 20-428

Dear Dr. Wilkin:

Allergan hereby submits in accordance with 21 CFR 314.70(b)(2)(viii) a supplement to the above-referenced new drug application. In this supplement, we seek authorization of a new tube size, 50 grams. AZELEX® (azelaic acid cream) 20% is currently marketing in 5 and 30 gram sizes. In addition, we are seeking modification to the content uniformity test method and evaluation criteria; and an adjustment to the micropenetration specification.

The 50 gram size will be packaged in the same container/closure system as the 30 gram size and supplied by the same NDA-approved manufacturer The approved container/closure system is an aluminum tube with an epoxide internal coating, and an end seal band of a polyamide combination, as well as a high density polyethylene white screw cap.

Three batches of AZELEX® Cream were manufactured by and filled into 50 gram tubes. One batch was filled into 30 gram tubes and used as a control. The control lot and the three qualification lots were monitored for a period of six months at the % RH storage condition and three months at the % RH storage condition. All data, with the exception of azelaic acid content uniformity and micropenetration, are within the product specifications through the study periods.

The AZELEX® Cream content uniformity data for the qualification lot 98C02 and the control lot 98C03 were found to be out of specification after six months of storage at % RH according to the rigorous criteria described in the approved product shelf life specification listed below:

> Mean of all 12 injections (2 tubes, 3 weighings per tube, double injection per weighing) shall fall within % of label claim (% w/w). All 12 injections shall fall within % of label claim (% w/w).

An investigation was conducted regarding the content uniformity test methodology. The control lot and qualification lots were subsequently analyzed based on the requirements set forth in the compendial method, United States Pharmacopeia, Chapter <905>, "Uniformity of Dosage Units: Content Uniformity-Capsules, Transdermal Systems, Inhalations, and Molded Tablets" (listed below), and were found to meet the criteria.

a. Not less than 9 of 10 assay results [3 tubes, 3 weighings per tube (top, middle, and bottom), one injection per weighing; and a tenth assay point from the central third of the last tube] lies within the range of % of the label claim.
b. No assay is outside the range of % of the label claim.
c. The RSD of the 10 assay values is less than or equal to %.

If conditions a, b and c are met a test result of PASS is assigned to the content uniformity test. If 2 or 3 assays are outside of the range of % of the label claim, or if the RSD is greater than %, or if both conditions prevail, an additional 20 assays may be performed using six additional containers using the same sampling criteria listed above.

d. Not less than 27 of 30 assay results lies within the range of % of the label claim.
e. No assay is outside the range of % of the label claim.
f. The RSD of the 30 assay values is less than or equal to %.

If the above criteria are not met, a test result of Fail is assigned to the content uniformity.

Allergan recognized the utility of the compendial testing methodology and evaluation criteria when applied to semi-solids and developed SOP LAB-10 based on those requirements (attachment 2). The proposed criteria will be applied to content uniformity for azelaic acid and benzoic acid (with slightly different ranges) since the assay results for both determinations are generated from one sampling.

The micropenetration data for lot 98C02 were found to be above specification after three and six months of storage at % RH. The data were consistent with micropenetration data observed by Allergan's testing facility in Ireland during the ongoing stability program for product in the approved market configuration. The high results on micropenetration represent a very slight and insignificant change in the viscosity of AZELEX® Cream and do not effect the safety and efficacy of the product, according to John Sefton, Ph.D., Director, Dermatology Clinical Research (attachment 3).

As a result of a micropenetration stability deviation investigation, Allergan proposes the addition of a certified viscosity standard to the testing method [as requested by the FDA in the deficiency letter of August 8, 1995 (attachment 4)], and an adjustment to the micropenetration specifications from mPa*s(milli Pascal second or centipoise). Correlation between penetration and viscosity have been established and supported in literature (attachment 5). Viscosity Standards were identified as appropriate reference standards to be included in the micropenetration method. By incorporating the Viscosity Standards as reference standards the results for the micropenetration can be normalized and expressed as "Yield Value".

When evaluated against the proposed micropenetration specification, micropenetration data expressed as "Yield Value" were found to be satisfactory and comparable to the product in the approved 30 gram aluminum tube configuration. Furthermore, all accelerated stability data for the qualification lots were found to be comparable to the control lot throughout the periods studied.

The stability profiles for azelaic acid and benzoic acid for the qualification lots were found to be equivalent to the 30 gram (control) data.

Therefore, we are submitting the information listed below to support the new package size, modified content uniformity method, and new micropenetration specification.

1. Comparison Table of Current and Proposed Product Final and Shelf Life Specifications
2. Allergan R&D SOP LAB-10
3. John Sefton, Ph.D., Director, Dermatology Clinical Research, Memorandum of 10/29/96
4. FDA Deficiency Letter, August 8, 1995
5. Correlation of Micropenetration and Viscosity for AZELEX® Cream
6. Stability Protocol for Qualification
7. Technical Report # PA-1997-027
8. Drawings and Packaging Specifications
9. Draft Labeling
10. Tube Supplier DMF

We trust that this information will be satisfactory for your review and approval of the supplement for AZELEX® (azelaic acid cream) 20%, NDA 20-428.

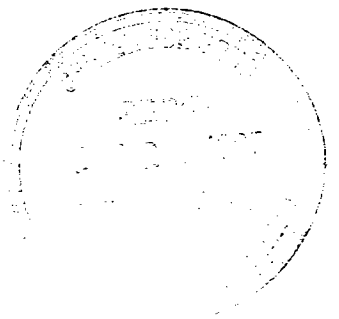
Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

ORIGINAL

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



SC5-006 BC
NDA SUPPLEMENT

August 28, 1997

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: AZELEX® (azelaic acid cream) 20%
NDA 20-428 [S-006]

Dear Dr. Wilkin:

Allergan hereby submits an amendment to the supplement submitted on August 5, 1997 to the above-referenced new drug application. This amendment is to correct an error in the Technical Report #PA-1997-027 entitled, "Stability Report for 50 gram Aluminum Tube Qualification of AZELEX® (azelaic acid cream) 20%, Formula 8466X" [Attachment 7]. The error was made in reporting the stability conditions used for storage of product (for micropenetration assay only) at the European Technical Center (ETC). The correct conditions are % relative humidity (RH).

Please remove the affected pages and replace them with the attached corrected pages [Pages 1, 3, 5, and 6 of 7 in Attachment 7]. All corrections are highlighted.

We apologize for this error, and trust that this corrected information will be satisfactory for your review and approval of the supplement for AZELEX® (azelaic acid cream) 20%, NDA 20-428.

Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

enclosures

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

SNE-006
SUPPL NEW CORRESP

February 5, 1998

ORIGINAL

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: AZELEX® (azelaic acid cream) 20%
NDA 20-428/S-006
Intent to file an amendment

Dear Dr. Wilkin:

In response to your not-approvable letter dated January, 1998 (the exact date is obscured), Allergan informs the Agency that we intend to amend our supplement to address the issues raised in your letter. The amendment will be formally submitted as soon as feasible after review and evaluation of the data.

Sincerely,

Stephen Buxbaum
Director
Worldwide Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 23 1997

NDA 20-428/S-007

Allergan Herbert Division of Allergan Inc.
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92623-9534

Dear Mr. Buxbaum:

Please refer to your August 13, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex® (azelaic acid cream) Cream, 20%.

The supplemental application provides for changing the azelaic acid assay specification as follows:

FROM	%
TO	%

We have completed the review of this supplemental application and it is approved, effective as of the date of this letter.

This approval affects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Olga Cintron, R.Ph.
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

/S/ 9/22/97

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, DNDC III
Division of Dermatologic and Dental Drug Products (HFD-540)
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Original NDA 20-428
HFD-540/Div. Files
HFD-830/CChen
HFD-80
HFD-40/DDMAC
DISTRICT OFFICE
HFD-540/CSO/OCintron
HFD-540/Chem/WTimmer
HFD-540/ChemTeamLdr/WHDeCamp

APPROVED

SEP 20 1997

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

SEP 23 1997

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 **CHEM.REVIEW #**: 1 **REVIEW DATE**: 05-SEP-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SCS-007	13-AUG-97	15-AUG-97	05-SEP-97

NAME & ADDRESS OF APPLICANT: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, C 92623-9534

Stephen Buxbuam
Director
Worldwide Regulatory Affairs
(714) 246-4534

DRUG PRODUCT NAME

Proprietary:	AZELEX™ (azelaic acid cream) 20%
Nonproprietary/USAN:	azelaic acid cream 20%
Code Names/#'s:	AGN191861
Chemical Type/ Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status:

PHARMACOLOGICAL INDICATION: Acne Vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: __X__ R_x _____ **OTC**

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

NAME: Azelaic Acid
CHEMICAL NAME: Nonanedioic Acid
SYNONYMS: Lepargylic Acid, Anchoic Acid
CAS NUMBER: 123-99-9
MOLECULAR WEIGHT: 182.22
CHEMICAL FORMULA: $C_9H_{16}O_4$
STRUCTURAL FORMULA: $HO_2C(CH_2)_7CO_2H$

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS:

This supplement was submitted to relax the active ingredient specification:

FROM: %

TO: %

A graph of azelaic acid assay shows that the *mean* values fall within the tight ±5% limit. However, changing the azelaic acid specification to the conventional % limit will allow for individual assay variability. In addition, the current stability program indicates that the individual assays will remain close to the ±5% limit.

CONCLUSIONS & RECOMMENDATIONS:

The supplement application is approvable for manufacturing and controls under section 505 of the FFD&C Act.

/S/

William C. Timmer, Ph.D.
Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/Chem/WCTimmer
HFD-540/TmLdr/WHDeCamp
HFD-540/CSO/OCintron

9/23/97

filename: c:\wpwin61\wpdocs\cder\supplmnt\n20428-c.007

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-428/S-007

Allergan Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUG 18 1997

Attention: Stephen Buxbaum
Director Worldwide, Regulatory Affairs

Dear Mr. Buxbaum:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Azelex® (azelaic acid cream) 20%

NDA Number: 20-428

Supplement Number: S-007

Date of Supplement: August 13, 1997

Date of Receipt: August 15, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 14, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Dermatologic and Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Mary V. Kozma-Fornaro 8/18/97
Supervisor, Project Management Staff
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-428/S-007
HFD-540/Div. Files
HFD-540/CSO/Olga Cintron

SUPPLEMENT ACKNOWLEDGEMENT

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

ORIGINAL

August 13, 1997

NDA NO. 20428 SUPPL. NO. 007
NDA SUPPL NO. SCS

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: Azelex® (azelaic acid cream) 20%
NDA 20-428
Supplement: Change of Regulatory Specification

Dear Dr. Wilkin:

Allergan hereby submits, in accordance with 21 CFR 314.70(b)(2)(ii), a supplement to the above-referenced new drug application. In this supplement, we seek authorization to adjust the active ingredient specification for azelaic acid in the finished product:

From:	%
To:	%

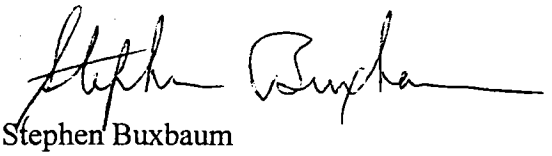
The specification was inadvertently registered as ±5% both at release (time of manufacture) and end of shelf. This arose from the fact that the product was developed by for European markets, who sometimes impose narrower limits. The narrow specification is not a normal practice in the United States for a finished product, and it constitutes an unnecessary burden.

A graph of azelaic acid assay results (Attachment 1) from 6 recently manufactured lots of product in the on-going stability program (Attachment 2), illustrates the distribution of data over time within the specification. Some of the individual stability data points are at the upper or lower limit of the current specification. Although the mean values fall within the tight ±5% limits, changing the azelaic acid specification to the conventional % of label claim will allow for individual assay variability and the not-unexpected decrease in azelaic acid concentration over time.

This change only affects the azelaic acid specification; it does not affect the regulatory analytical method.

We trust that this information will be satisfactory for your review and approval of this supplement for AZELEX® (azelaic acid cream) 20%, NDA 20-428.

Sincerely,



Stephen Buxbaum
Director
Worldwide Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 17-970/S-024

Trade Name:NOLVADEX TABLES

Generic Name:(tamoxifen citrate)

Sponsor: Zeneca, Inc.

Approval Date: April 1, 1993

Indication: Provides for the use of tamoxifen in the treatment of metastatic breast cancer in males.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 17-970/S-024

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter	X			
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)			X	
EA/FONSI			X	
Pharmacology Review(s)	X			
Statistical Review(s)			X	
Microbiology Review(s)			X	
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)	X			
Administrative Document(s)			X	
Correspondence			X	

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 17-970/S-024

APPROVAL LETTER

DF

APR - 1 1993

NDA 17-970/S-024/S-026/S-022/S-025

Zeneca, Inc.
Concord Pike & New Murphy Road
Wilmington, Delaware 19897

Attention: William J. Kennedy, Ph.D.
Vice-President, Drug Regulatory Affairs

Dear Dr. Kennedy:

Reference is made to your supplemental new drug application (S-024) dated May 22, 1992 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nolvadex (tamoxifen citrate) Tablets.

We also refer to your February 1, 1993 amendment which responds to our December 17, 1992 approvable letter. Reference is also made to your additional communications dated March 17 and 19, 1993.

The supplemental application provides for the use of tamoxifen in the treatment of metastatic breast cancer in males.

We have completed our review of this supplemental application as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling dated January 1993. Accordingly, the application is approved, effective as of the date of this letter.

We acknowledge your March 19, 1993 commitment to make the following changes at the next label printing which may be submitted as a supplemental application under the provisions of 21 CFR 314.70(c)(2).

1. In the last paragraph of the CLINICAL PHARMACOLOGY section
will be changed to

2. The following will be added to the last paragraph of the ADVERSE REACTIONS section concerning male safety profiles.

3. In the OVERDOSAGE section

will be changed to

In addition, please note the following.

4. We recommend including the names of the three trials in the labeling to identify the 4,000 patients mentioned in the new paragraph in the WARNINGS section. The sentence could state "However, in the controlled studies involving nearly 4,000 patients (Scottish, Christie Hospital and Danish trials), there was no significant increase in the incidence of uterine cancer in patients receiving NOLVADEX.

This approved supplement supersedes your supplemental application (S-026) dated November 25, 1992 providing for changes in the WARNINGS section concerning the incidences of endometrial cancer and a complete revision of the OVERDOSAGE section. In addition, supplemental application (S-022) dated April 6, 1992, providing for changes in the PRECAUTIONS section concerning patients with preexisting leukopenia and thrombocytopenia and supplemental application (S-025) dated September 17, 1992, providing for changes in the WARNINGS and ADVERSE REACTIONS sections concerning hepatic toxicities and changes in the ADVERSE REACTIONS section concerning hair thinning and/or partial hair loss are also superseded. We note that these changes were put into effect under 21 CFR 314.70(c) and, therefore, the supplements will be retained as part of the application.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Gregory Burke, M.D., Ph.D.
Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig. NDA 17970/S-024/S-026/S-022/S-025
HFD-150/Division File
HFD-151/PZimmerman/3-19-93/3-23-93 3/23/93
HFD-80
HFC-130
HFD-632
HFD-730
HFD-100/500
HFD-150/AChen
HFD-150/RJustice
R/D Init. by: AChen/3-19-93
RJustice/3-19-93
JRJohnson/3-19-93
RGScully/3-19-93
JDeGeorge/3-19-93
MMehta/3-19-93

3/31/93

SUPPLEMENTAL NDA APPROVAL/S-024
ACKNOWLEDGE RETAIN/S-022/S-025/S-026

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 17-970/S-024

APPROVABLE LETTER

DEC 17 1992

NDA 17-970/S-024

ICI Pharmaceuticals Group
Concord Pike & New Murphy Road
Wilmington, Delaware 19897

Attention: William J. Kennedy, Ph.D.
Vice-President, Drug Regulatory Affairs

Dear Dr. Kennedy:

Reference is made to your supplemental new drug application (S-024) dated May 22, 1992 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nolvadex (tamoxifen citrate) Tablets.

We also acknowledge your additional September 16 and October 13 and 28, 1992 communications.

The supplemental application provides for the use of tamoxifen in the treatment of metastatic breast cancer in males.

We have completed our review of this supplemental application, submitted with draft labeling, and it is approvable. Before the supplemental application may be approved, however, the labeling must be revised. New draft labeling should be submitted to include the following revisions.

Redacted 1

pages of trade secret and/or confidential commercial information

Please submit in duplicate, the advertising copy which you intend to use on your promotional and/or advertising campaign. Please submit one copy to the Division of Oncology and Pulmonary Drug Products and a second directly to:

Division of Drug Marketing, Advertising and Communications
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission. This form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Sincerely yours,

Gregory Burke, M.D., Ph.D.
Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig NDA
DIV file
HFD-150 - Zimmerman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 17-970/S-024

FINAL PRINTED LABELING

64033-06

Rev W 01/93

APPROVED

APR 1 1993

PROFESSIONAL INFORMATION BROCHURE

10 MG TABLETS

Nolvadex®

NDA # TAMOXIFEN CITRATE 021

17970

NDA SUPPL FOR SES (AF)

WORKING COPY

Labeling: 10/93

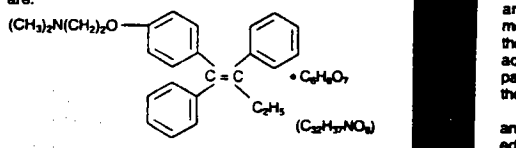
NDA dtd: 17970 Rec'd 2/4/93

Reviewed by: Paul E. Bunn 4/1/93

DESCRIPTION

NOLVADEX® (tamoxifen citrate) Tablets for oral administration contain 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg of tamoxifen. It is a nonsteroidal antiestrogen.

Chemically, NOLVADEX is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z)2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3- propanetricarboxylate (1:1). The structural and empirical formulas are:



$(C_{32}H_{37}NO_8)$

Tamoxifen citrate has a molecular weight of 563.62, the pKa' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C, it is 0.2 mg/mL.

NOLVADEX is intended only for oral administration; the tablets should be protected from heat and light.

Inactive Ingredients: carboxymethylcellulose calcium, magnesium stearate, mannitol, starch.

CLINICAL PHARMACOLOGY

NOLVADEX is a nonsteroidal agent which has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.

In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein. Preliminary pharmacokinetics in women using radiolabeled tamoxifen has shown that most of the radioactivity is slowly excreted in the feces, with only small amounts appearing in the urine. The drug is excreted mainly as conjugates, with unchanged drug and hydroxylated metabolites accounting for 30% of the total.

Blood levels of total radioactivity following single oral doses of approximately 0.3 mg/kg reached peak values of 0.06-0.14 µg/mL at 4-7 hours after dosing, with only 20%-30% of the drug present as tamoxifen. There was an initial half-life of 7-14 hours with secondary peaks four or more days later. The prolongation of blood levels and fecal excretion is believed to be due to enterohepatic circulation.

Two studies (Hubay and NSABP B-09) demonstrated an improved disease-free survival following radical or modified radical mastectomy in postmenopausal women or women 50 years of age or older with surgically curable breast cancer with positive axillary nodes when NOLVADEX was added to adjuvant cytotoxic chemotherapy. In the Hubay study, NOLVADEX was added to "low-dose" CMF (cyclophosphamide, methotrexate and fluorouracil). In the NSABP B-09 study, NOLVADEX was added to melphalan [L-phenylalanine mustard (P)] and fluorouracil (F).

Tumor hormone receptors may help predict which patients will benefit from the adjuvant therapy, but not all breast cancer adjuvant NOLVADEX studies have shown a clear relationship between hormone receptor status and treatment effect. In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50-59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while there was a nonstatistically significant trend toward adverse effect in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60-70 years, there was a trend toward a beneficial effect of NOLVADEX without any clear relationship to estrogen or progesterone receptor status.

Three prospective studies (ECOG-1178, Toronto, NATO) using NOLVADEX adjuvantly as a single agent demonstrated an improved disease-free survival following total mastectomy and axillary dissection for postmenopausal women with positive axillary nodes compared to placebo/no treatment controls. The NATO study also demonstrated an overall survival benefit.

One prospective, double-blind, randomized study (NSABP-14) demonstrated a significant improvement in disease-free survival for NOLVADEX compared to placebo when used adjuvantly following total mastectomy and axillary dissection or segmental resection, axillary dissection, and breast radiation in women with axillary node-negative breast cancer whose tumors were estrogen receptor positive (≥ 10 fmol/mg cytosol protein). The benefit was apparent in both women under age 50 and those aged 50 years or more. One additional randomized study (NATO) demonstrated improved disease-free survival for NOLVADEX compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of NOLVADEX appeared to be independent of estrogen receptor status.

Three prospective, randomized studies (Ingle, Pritchard, Buchanan) compared NOLVADEX to ovarian ablation (oophorectomy or ovarian irradiation) in premenopausal women with advanced breast cancer. Although the objective response rate, time to treatment failure, and survival were similar with both treatments, the limited patient accrual prevented a demonstration of equivalence. In an overview analysis of survival data from the three studies, the hazard ratio for death (NOLVADEX/ovarian ablation) was 1.00 with two-sided 95% confidence intervals of 0.73 to 1.37. Elevated serum and plasma estrogens have been observed in premenopausal women receiving NOLVADEX. However, the data from the randomized studies do not suggest an adverse effect. A limited number of premenopausal patients with disease progression during NOLVADEX therapy responded to subsequent ovarian ablation.

Published results from 122 patients (119 evaluable) and clinical responses in 16 patients (13 evaluable) treated with NOLVADEX have shown that NOLVADEX is effective for the palliative treatment of male breast cancer. Sixty-six of these 132 evaluable patients responded to NOLVADEX which constitutes a 50% objective response rate.

INDICATIONS AND USAGE

Adjuvant Therapy: NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection or segmental mastectomy, axillary dissection, and breast irradiation in women with axillary node-negative breast cancer. Data are insufficient to predict which women are most likely to benefit and to determine if NOLVADEX provides any benefit in women with tumors less than 1 cm.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T_{1-3}, N_1, M_0). In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

The estrogen and progesterone receptor values may help to predict whether adjuvant NOLVADEX therapy is likely to be beneficial.

Therapy for Advanced Disease: NOLVADEX is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, NOLVADEX is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

CONTRAINDICATIONS

NOLVADEX is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Visual disturbance including corneal changes, cataracts and retinopathy have been reported in patients receiving NOLVADEX.

As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.

A small number of cases of endometrial hyperplasia and endometrial polyps have been reported in association with NOLVADEX treatment. A definitive relationship to NOLVADEX therapy has not been established.

In a large randomized trial in Sweden of adjuvant NOLVADEX 40 mg/day for 2-5 years, an increased incidence of endometrial cancer was noted. Thirteen of 931 NOLVADEX treated patients versus 2 of 915 controls developed cancer of the body of the uterus [RR = 6.4 (1.4 - 28). P < 0.01]. After approximately 7 years of follow-up in the ongoing NSABP B-14 trial, 9 of the 1,439 women randomized to receive NOLVADEX developed Stage I endometrial cancer. Two of the 1,440 women randomized to receive placebo, who subsequently had recurrent breast cancer and were treated with NOLVADEX, also developed Stage I endometrial cancer. However, in the other controlled studies involving nearly 4,000 patients, there was no significant increase in the incidence of uterine cancer in patients receiving NOLVADEX. Patients receiving NOLVADEX should have routine gynecological care and report any abnormal vaginal bleeding to their physician.

In the same Swedish trial, the incidence of second primary breast tumors was reduced in the tamoxifen arm (P < 0.05). In the NSABP B-14 trial in which patients were randomized to NOLVADEX 20 mg/day for 5 years versus placebo, the incidence of second primary breast cancers is also reduced.

NOLVADEX has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to NOLVADEX is uncertain. However, some positive rechallenges and dechallenges have been reported.

Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX and should use barrier or nonhormonal contraceptive measures. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well-controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General: NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been reported. Decreases in platelet counts, usually to 50,000-100,000/mm³, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to NOLVADEX therapy.

Information for Patients: Women taking NOLVADEX should be instructed to report abnormal vaginal bleeding which should be promptly investigated.

Laboratory Tests: Periodic complete blood counts, including platelet counts, may be appropriate.

Drug Interactions: When NOLVADEX is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

Drug/Laboratory Testing Interactions: During post-marketing surveillance, T_4 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by clinical hyperthyroidism.

(CONTINUED ON REVERSE SIDE)

NOLVADEX® (tamoxifen citrate)

Variations in the karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given NOLVADEX.

In the postmarketing experience with NOLVADEX, infrequent cases of hyperlipidemias have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with pre-existing hyperlipidemias.

Carcinogenesis: A conventional carcinogenesis study in rats (doses of 5, 20, and 35 mg/kg/day for up to 2 years) revealed hepatocellular carcinoma at all doses, and the incidence of these tumors was significantly greater among rats given 20 or 35 mg/kg/day (69%) than those given 5 mg/kg/day (14%). The incidence of these tumors in rats given 5 mg/kg/day (29.5 mg/m^2) was significantly greater than in controls.

In addition, preliminary data from 2 independent reports of 6-month studies in rats reveal liver tumors which in one study are classified as malignant.

Endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

Mutagenesis: No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

Impairment of Fertility: Fertility in female rats was decreased following administration of 0.04 mg/kg for two weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7-17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6-18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was obtained by comparing dosed animals with controls of another study.

The recommended daily human dose of 20-40 mg corresponds to 0.4-0.8 mg/kg for an average 50 kg woman.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

Adverse reactions to NOLVADEX are relatively mild and rarely severe enough to require discontinuation of treatment. If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

In patients treated with NOLVADEX for metastatic breast cancer, the most frequent adverse reactions to NOLVADEX are hot flashes and nausea and/or vomiting. These may occur in up to one-fourth of patients.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache and hair thinning and/or partial hair loss.

There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxic agents are combined with NOLVADEX.

NOLVADEX has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestatis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to NOLVADEX is uncertain. However, some positive rechallenges and dechallenges have been reported.

Ovarian cysts have been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with NOLVADEX.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with NOLVADEX as compared to placebo.

In the ongoing NSABP study-B-14, women with axillary node-negative breast cancer were randomized to 5 years of NOLVADEX or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of 29 months). The incidence of hot flashes (57% v 41%), vaginal discharge (24% v 12%), and irregular menses (19% v 15%) were higher with NOLVADEX compared with placebo. The incidence of all other adverse effects were similar in the two treatment groups with the exception of thromboembolic events (phlebitis), which although rare, were more common with NOLVADEX than with placebo.

NSABP B-14 STUDY

Adverse Effect	No. of Women (%) NOLVADEX (n=1376)		Placebo (n=1396)	
Hot Flashes	787	(57)	566	(41)
Fluid Retention	339	(25)	326	(23)
Vaginal discharge	330	(24)	160	(12)
Irregular menses	264	(19)	203	(15)
Nausea	255	(19)	235	(17)
Skin rash	180	(13)	150	(11)
Diarrhea	106	(8)	129	(9)
Vomiting	25	(2)	16	(1)
Phlebitis	15	(1)	2	(<1)
Thrombocytopenia*	10	(1)	4	(<1)
Leukopenia**	7	(1)	10	(1)

*Defined as a platelet count of <100,000/mm^3
**Defined as a white blood cell count of <3000/mm^3

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, NOLVADEX or placebo was administered for 2 years to women following mastectomy. When compared to placebo, NOLVADEX showed a significantly higher incidence of hot flashes (19% versus 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment groups with the exception of thrombocytopenia where the incidence for NOLVADEX was 10% versus 3% for placebo, an observation of borderline statistical significance.

The other adverse reactions reported equally in the ECOG study for NOLVADEX and placebo include abnormal renal function tests, fatigue, dyspnea, anorexia, cough, and abdominal cramps. A relationship of these reactions to the administration of NOLVADEX has not been demonstrated since the frequency was not significantly different from that reported in placebo treated women.

In other adjuvant studies, Toronto and NOLVADEX Adjuvant Trial Organization (NATO), women received either NOLVADEX or no therapy. In the Toronto study, hot flashes and nausea and/or vomiting were observed in 29% and 19% of patients, respectively, for NOLVADEX versus 1% and 0% in the untreated group. In the NATO trial, hot flashes, nausea and/or vomiting and vaginal bleeding were reported in 2.8%, 2.1% and 2.0% of women, respectively, for NOLVADEX versus 0.2% for each in the untreated group.

The following table summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared NOLVADEX therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

Adverse Reactions*	NOLVADEX All Effects Number of Women (%) n = 104		OVARIAN ABLATION All Effects Number of Women (%) n = 100	
Flush	34	(32.7)	46	(46)
Amenorrhea	17	(16.3)	69	(69)
Altered Menses	13	(12.5)	5	(5)
Oligomenorrhea	9	(8.7)	1	(1)
Bone Pain	6	(5.7)	6	(6)
Menstrual Disorder	6	(5.7)	4	(4)
Nausea	5	(4.8)	4	(4)
Cough/Coughing	4	(3.8)	1	(1)
Edema	4	(3.8)	1	(1)
Fatigue	4	(3.8)	1	(1)
Musculoskeletal Pain	3	(2.8)	0	(0)
Pain	3	(2.8)	4	(4)
Ovarian Cyst(s)	3	(2.8)	2	(2)
Depression	2	(1.9)	2	(2)
Abdominal Cramps	1	(1)	2	(2)
Anorexia	1	(1)	2	(2)

*Some women had more than one adverse reaction.

NOLVADEX is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of NOLVADEX in males is similar to that seen in women.

OVERDOSAGE

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3-5 days of beginning NOLVADEX and cleared within 2-5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of NOLVADEX given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of NOLVADEX given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 8 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

In women and men with metastatic breast cancer, one or two 10 mg tablets are administered twice a day (morning and evening). In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years (See CLINICAL PHARMACOLOGY). In B-14, the ongoing NSABP adjuvant study in women, one 10 mg NOLVADEX tablet is being given twice a day for five years. The optimal duration of adjuvant therapy is not known.

HOW SUPPLIED

Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light. NDC 0310-0600.

ICI Pharma
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA
64033-06
Rev W 01/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 17-970/S-024

MEDICAL REVIEW(S)

VF

MEDICAL OFFICER REVIEW OF LABELING SUPPLEMENT

NDA: 17-970/S-024
DRUG: tamoxifen citrate tablets (Nolvadex)
APPLICANT: Zeneca Pharmaceuticals Group
DATE: July 30, 1993

On April 22, 1993, the applicant submitted final printed labeling which was revised as provided for under 21 CFR 314.70(3)(c). The warning concerning hepatic toxicities was revised as requested in our letter of December 17, 1992 (S-024). In addition, the two paragraphs concerning drug interactions with phenobarbital and bromocriptine were moved to the **Drug Interactions** subsection of the **PRECAUTIONS** section

RECOMMENDED REGULATORY ACTION

The labeling changes should be approved. However, the labeling should also be revised to incorporate the deficiencies listed in the review of the changes in the **Pregnancy Category D** and **Mutagenesis** subsections that were communicated to the applicant by facsimile on June 3, 1993.

/S/

Robert L. Justice, M.D.

John R Johnson MD
8-2-93

cc:
Orig NDA 17-970/S-024/S-014
HFD-150/Div File
HFD-150/RJustice
HFD-151/PZimmerman
HFD-340
Works File 17970S24.WPS

ADDENDUM TO REVIEW OF DRAFT LABELING

DEC 10 1992

NDA: 17-970/S-024
Drug: Nolvadex (tamoxifen citrate) tablets
Sponsor: ICI Pharmaceuticals Group
Date: December 10, 1992

The draft labeling for the male breast cancer supplement was originally reviewed in the Medical Officer Review of December 2, 1992. In addition to the labeling comments in that review, the DOSAGE AND ADMINISTRATION section should also be revised as follows for clarity:

> In women and men with metastatic breast cancer, one or two 10 mg tablets is administered twice a day (morning and evening). In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years (See Clinical Pharmacology).
>
> The optimal duration of adjuvant therapy is not known.

Recommended Regulatory Action

The additional labeling change should be communicated to the sponsor.

/S/

Robert L. Justice, M.D.

JR Johnson MD
12-10-92

Orig. NDA 17-970/S-024
HFD-150/Div. File
HFD-150/RJustice
HFD-151/PZimmerman
Works File TAMLBL

Medical Officer Review of a Supplemental NDA

DEC 17 1992

NDA: 17-970/S-024

Applicant: ICI Pharmaceuticals Group
Division of ICI Americas Inc.
Wilmington, Delaware 19897

Date of Revision: December 2, 1992

I. General Information

A. Name of Drug

(1) Generic: Tamoxifen Citrate

(2) Trade: Nolvadex

B. Pharmacologic Category: Antiestrogen

C. Proposed Indication:

1. "Nolvadex is effective in the treatment of metastatic breast cancer in women and men."

2. "Limited data from spontaneous and literature reports of the use of Nolvadex in treating male breast cancer patients have revealed that Nolvadex is effective in delaying recurrence following mastectomy and breast irradiation in men with axillary node-positive breast cancer."

D. Dosage Form

Tablets for oral administration contain 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg of tamoxifen.

E. Route of Administration

Oral

F. Related IND:

G. This review includes submissions from May 22, September 16, October 13 and 28, 1992.

II. Manufacturing Controls

Approved drug

III. Pharmacology

Approved drug

The only differences in toxicities seen in the female and male rats given tamoxifen 5 - 35 mg/kg/day for 104 - 107 weeks were in the genitourinary tract. At autopsy, the male rats had atrophy of their testes, epididymides, prostate and seminal vesicles.

IV. Clinical Background

A. Approved Indications

1. Adjuvant Therapy

"Nolvadex is effective in delaying recurrence following total mastectomy and axillary dissection or segmental mastectomy, axillary dissection, and breast irradiation in women with axillary node-negative breast cancer. Data are insufficient to predict which women are most likely to benefit and to determine if Nolvadex provides any benefit in women with tumors less than 1 cm. Nolvadex is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T_{1-3}, N_1, M_0). In some Nolvadex adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

The estrogen and progesterone receptor values may help to predict whether adjuvant Nolvadex therapy is likely to be beneficial. "

2. Therapy for Advanced Disease

Nolvadex is effective in the treatment of metastatic breast cancer in women. In premenopausal women with metastatic breast cancer, Nolvadex is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from Nolvadex therapy."

B. Male Breast Cancer

Carcinoma of the breast in males accounts for 1% of all breast cancer and 0.2% of malignant tumors in men (Crichlow RW, Galt SW. Surgical Clinics of North America 70(5): 1165-117, 1990). The mean age at

diagnosis is approximately 10 years older than in women. Male breast cancer does not have the bimodal distribution seen in female breast cancer. The incidence of male breast cancer has been stable over the last fifty years.

Men with Klinefelter syndrome have an increased risk of having breast cancer. Because of the paucity of cases, the incidence is estimated to be around 3-6% (Evans DB, Crichlow RW. CA-a Cancer Journal for Clinicians 37(4): 246-251, 1987). Hyperestrogenism may be a causative factor. Testicular injuries from trauma or temperature exposure in men who worked in mills and around blast furnaces result in a higher incidence of breast cancer. Also, because of liver damage secondary to schistosomiasis, breast cancer in men is more common than prostate cancer in Egypt (Borgen PI. Seminars in Surgical Oncology 7: 314-319, 1991). However, men treated with estrogen for prostate cancer had no increased incidence of breast cancer. Other risk factors that have been associated with male breast cancer are gynecomastia, family history, radiation, and elevated prolactin level.

The histologies are similar to those seen in women, except lobular carcinoma *in situ* does not occur in men. Also, bilaterality is rarer in men. Eighty-five percent of male breast cancers express estrogen receptors, and 69% express progesterone receptors. The natural history of the disease is similar to that in women.

There is some evidence that stage for stage the prognosis is worse in male than female breast cancer. The five-year and ten-year survival rates for the node negative patients are 77% and 65%, respectively. Positive nodes decreased the five- and ten-year survival rates to 46% and 14%, respectively (Crichlow RW and Galt SW: Male Breast Cancer. Surgical Clinics of North America 70(5): 1165-1177, 1990). However, studies reported by Heller and colleagues reported no differences between males and females at five years. The ten-year survival for males with Stage I disease was also similar to that for females (Heller KS, Rosen PP, Schottenfeld D et al: Male breast Cancer: A clinicopathologic study of 97 cases. Ann Surg 18860-65, 1978). A difference in ten-year survival was found only in males with positive nodes. A delay in presentation and diagnosis may contribute to the poor prognosis.

C. Advanced Male Breast Cancer

Because of the small number of cases, no randomized trials have been conducted in the treatment of male breast cancer. Surgery is still the main form of treatment for local disease. Radiation has been added as neoadjuvant therapy to minimize the surgical procedure or as adjuvant therapy to decrease local recurrence. Orchiectomy had been the first-line therapy for advanced disease but is not widely accepted by patients. The response to orchiectomy is 55% (Crichlow RW, Galt SW. Surgical Clinics of North America 70(5): 1165-1177, 1990). Other ablative hormonal therapies that have been used are adrenalectomy with a 74% response rate, and hypophysectomy with an equal response rate. However, these are surgical procedures that are not widely used and there are a small number of patients in each series. Additive hormonal therapy used includes buserelin with and without flutamide, estrogen, steroids, androgens, and tamoxifen.

V. Uncontrolled Clinical Trials for Advanced Breast Cancer

Because of the small number of patients with this disease, it is very difficult to conduct a randomized clinical trial. In September 1991, ICI approached the FDA regarding the approval of a supplemental Nolvadex indication using case reports and published literature to support its use in male breast cancer. The FDA was receptive to use of this approach for a supplemental indication in an uncommon malignancy where no standard life-prolonging or curative therapy exists. This supplement consists of a collection of 24 case reports by Dr. Ribeiro and 16 cases reported to the ICI under their general protocol. The protocol was generated in 1977 for collecting male breast cancer data.

A. The Protocol

The protocol was not included with the original NDA submission. ICI submitted the protocol at our request on 9/16/92. This protocol was activated in August 29, 1979.

1. Objectives

None listed

2. Eligibility Criteria

Men with advanced stage histologically confirmed breast cancer. The disease had progressed after conventional methods of therapy for breast cancer.

3. Treatment Schedule

The recommended dose was 10-20 mg bid. This dosing schedule was derived from data on treatment of women with breast cancer.

4. Case Reports

The physician was required to complete the male breast cancer case report form provided by ICI. All adverse reactions were to be reported on the case report form.

Reviewer's Comments

The protocol was written specifically to gather data on male breast cancer treated with tamoxifen in the United States. A lack of uniformity in staging, dosing, and follow-up is a fault of the loosely written protocol. Patients were not always followed to death. Uniform definitions of response and grading of toxicity were not provided. Patients were started on therapy prior to the initiation of the protocol.

B. Summary of Case Reports

Thirteen investigators from the USA and Canada reported sixteen cases of advanced male breast cancer treated with tamoxifen. These are presented in detail in the NDA. The information is not as uniform as those presented by Dr. Ribeiro. The ages ranged from years. Five presented with metastatic disease, eleven had recurrent disease and one was not reported. One patient had CNS disease. The interval between primary treatment and recurrence varied from months. Four patients received radiotherapy for recurrent disease. Thirteen patients had mastectomy as their primary surgical procedure. Six patients had chemotherapy prior to the administration of tamoxifen. Two patients received the chemotherapy as adjuvant therapy. Seven patients had orchiectomy and five refused orchiectomy. Four of these seven patients had additional hormonal therapies consisting of DES, premarin, adrenalectomy and clomid. Receptor status was known in only six patients: 4 ER/PR (+), 1 ER

(+)/PR (-), 1 ER/PR (-). Four patients received 40 mg/day of tamoxifen, and the rest were treated with 20 mg/day.

Three patients were not evaluable. One was treated for 2 days (Case 5) before dying of CNS disease; one patient had concomitant radiotherapy to site of measurable disease (Case 17); and one was treated with a combination of tamoxifen and Megace (Case 19). Three responses were seen in the remaining thirteen patients: 1 CR and 2 PR's. The duration of response ranged from days. One of the responders had recurred after orchiectomy. One of the PR's had pulmonary disease. Six patients were lost to follow-up. Seven patients had stable disease on therapy with duration ranging from years. (Table 1)

Table 1. Summary of ICI Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate)

ICI Case No.	Reporting Physician	Patient Age (yr)	Disease Site	Receptor Status[1]	Previous Treatment[2]	NOLVADEX (Tamoxifen Citrate) Daily Dose (mg)	Duration of Treatment (days)	Response Type[3]	Response Duration (Mo)	Comments
1	Dr. Aisner	47	Breast Lymph nodes Bone Lung	ER-positive PR-positive	CMF	30 20	21 188	NC	7	Patient initially refused orchiectomy and estrogen treatment. Patient had elective mastectomy after 4 months on NOLVADEX therapy.
2	Dr. Goudsmit	53	Lung Probably bone	ER-positive PR-positive	Mastectomy CMFP	20	60	PR	1	Patient refused orchiectomy, adrenalectomy and hypophysectomy. Patient lost to follow-up 2/6/79.
3	Dr. Legha	77	Breast Chest wall Anterior trunk Lymph nodes	ND	None	20	247	PR	6	Patient initially refused orchiectomy. Patient died of causes unknown but suspected to be cardiovascular.
4	Dr. Savlov	88	Skin Subcutaneous tissue Lymph nodes	ER-positive PR-negative	Mastectomy Orchiectomy	20	251	CR	7.3	Marked subjective improvement.
5	Dr. Escher	58	Bone Lung CNS	ND	Mastectomy Orchiectomy PREMARIN DES	20	2	-	-	Patient died of intracranial metastases 2 days after starting NOLVADEX treatment.
6	Dr. Godfrey	58	Lung	ND	Mastectomy Orchiectomy Adronalectomy CF	20	168	PROG	-	Subjective improvement.

[1] ER = estrogen receptor
PR = progesterone receptor
ND = not done

[2] C = cyclophosphamide
M = methotrexate
F = fluorouracil
P = prednisone
DES = diethylstilbestrol

[3] CR = complete response
PR = partial response
NC = no change
PROG = progression

Table 1 Summary of ICI Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

ICI Case No.	Reporting Physician	Patient Age (yr)	Disease Site	Receptor Status[1]	Previous Treatment[2]	NOLVADEX (Tamoxifen Citrate) Daily Dose (mg)	Duration of Treatment (days)	Response		Comments
								Type[3]	Duration (Mo)	
7	Dr. Kiang	48	Bone	ND	Mastectomy Orchiectomy CMF Prednisone Radiation therapy	40 then 30	Unknown	PROG	-	Patient lost to follow-up. Patient failed to respond to therapy on 2 occasions.
8	Dr. Kiang	77	Lung	ND	Bilateral mastectomy Radiation therapy Orchiectomy	40	244	NC	8	-
9	Dr. Witman	57	Lung	ND	Mastectomy	20	210	NC	7	Patient initally refused orchiectomy in favor of other palliative treatments. Patient lost to follow-up after 10/29/79.
10	Dr. Blom	[illegible]	Soft tissue Lymph nodes Bone	ND	None	20 40	56 280	NC	3.5	Improvement of lesions, less than PR after NOLVADEX therapy for 2 months. Treated with increased NOLVADEX dosage (40 mg/day) for 1.5 months. In addition, received CMF for 2 weeks, but stopped because of adverse events. Treatment continued with NOLVADEX and CYTOXAN (cyclophosphamide) for 6.5 months with PR. Patient not evaluable when CMF added to therapy.

[1] ND = not done

[2] C = cyclophosphamide
M = methotrexate
F = fluorouracil

[3] NC = no change
PROG = progression

Table 1 Summary of ICI Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

ICI Case No.*	Reporting Physician	Patient Age (yr)	Disease Site	Receptor Status[1]	Previous Treatment[2]	NOLVADEX (Tamoxifen Citrate) Daily Dose (mg)	Duration of Treatment (days)	Response		Comments
								Type[3]	Duration (Mo)	
11	Dr. Manni	70	Bone	ER-positive	Mastectomy	20	2,536	NC	83.4	Patient lost to follow-up after 11/19/86 with stable disease.
15	Dr. Lippman	70	Lung Soft tissue Lymph nodes	ND	Mastectomy CMF CLOMID	40	79 and 280	NC	15.2	Patient adamantly refused orchiectomy. Patient discontinued NOLVADEX for over 3 months on his own volition (also see adverse event table). Treated with CLOMID (clomiphene citrate) but discontinued because of adverse events. Restarted on NOLVADEX 6 weeks later. Patient died of breast cancer in September 1981.
16	Dr. Lippman	42	Lung Pancreas Brain Liver Bone	ND	Mastectomy CMF ADRIAMYCIN Radiation therapy Orchiectomy Adrenalectomy	40	19 and 3	PROG	-	Patient had extensive metastatic disease with a number of serum chemistry abnormalities and had undergone an array of therapies. Patient appeared to respond to adrenalectomy, thereby motivating the use of NOLVADEX. After less than one month of NOLVADEX therapy, the patient experienced adverse events concomitant with the therapy and poorly controlled diabetes.

* Patient (Dr. Arafah) were treated in an adjuvant setting.

[1] ER = estrogen receptor
ND = not done

[2] C = cyclophosphamide
M = methotrexate
F = fluorouracil

[3] NC = no change
PROG = progression

Table 1 Summary of ICI Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

ICI Case No.*	Reporting Physician	Patient Age (yr)	Disease Site	Receptor Status[1]	Previous Treatment	NOLVADEX (Tamoxifen Citrate) Daily Dose (mg)	Duration of Treatment (days)	Response		Comments
								Type[2]	Duration (Mo)	
17	Dr. Lippman	61	Soft tissue	ND	Bilateral mastectomy Radiation therapy Orchiectomy	40	53	-	-	Patient not evaluable-received electron-beam radiation therapy to chest wall and was being monitored for objective response.
19	Dr. Sutherland	76	Skin nodes	ER-negative PR-negative	Mastectomy	20	310	-	-	Patient is not evaluable; he was randomized and received NOLVADEX plus Megace in a postmenopausal breast cancer trial. Patient had initial complete response, then measurable progression after treatment with NOLVADEX and MEGACE (megestrol acetate).
21	Dr. Pearson	62	Bone	ER-positive PR-positive	Mastectomy	40	622	NC	17	Bone metatases stable for 17 months during NOLVADEX treatment. Received MEGACE for 4 months with progressive disease.

* Patients (Dr. Arafah) and patient 22 (Dr. Pearson) were treated in an adjuvant setting.

[1] ER = estrogen receptor
PR = progesterone receptor
ND = not done

[2] NC = no change

Toxicities reported were leukopenia, hypercalcemia, nausea, vomiting, diarrhea, increased pain, loss of libido, generalized weakness, increase in urination, headache, abdominal bloating, rash, fever with neurologic symptoms, and anorexia. Three of the thirteen evaluable patients discontinued therapy secondary to toxicities (Case 1, 7 and 16): nausea, vomiting, increased pain and diarrhea. (Table 2)

Table 2 Summary of Adverse Events - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate)

ICI Case No.*	NOLVADEX (Tamoxifen Citrate) Daily Dose (mg)	Adverse Events	Comments
1	20, then 40	Decrease in white blood cell count from 4,200 to 3,500/mm^3	NOLVADEX daily dose decreased to 20 mg.
	20	Severe lower back pain	NOLVADEX discontinued.
2	20	Abdominal pain, hypercalcemia suspected	NOLVADEX stopped for 2 days and then restarted without recurrence of abdominal pain.
3	20	None	-
4	20	None	-
5	20	Jacksonion seizure	Due to intracranial metastases.
6	20	None	-
7	40, then 30	Nausea, vomiting diarrhea, increased pain	NOLVADEX stopped and then restarted at 30 mg daily, but later discontinued because of "explained side effects."
8	40	Nausea and vomiting	NOLVADEX continued uninterrupted.
9	20	Shoulder pain	Markedly alleviated without therapy.
		CNS symptoms in left thumb	-
10	20, then 40	None stated	Patient stopped CMF chemotherapy because of adverse events that were not described.
11	20	None	-

* Patients were treated in an adjuvant setting.

Table 2. Summary of Adverse Events - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

ICI Case No.*	NOLVADEX (Tamoxifen Citrate) Daily Dose (mg)	Adverse Events	Comments
15	40	Generalized weakness, urinary incontinence, hesitancy	Patient discontinued NOLVADEX drug on his own volition because of symptoms noted.
		Generalized fatigue, abdominal bloating, pedal edema, blurring vision	Patient indicated increased edema since starting NOLVADEX.
		Dermatitis	Unknown cause.
		Paraparesis	Due to transverse myelopathy of unknown cause.
16	40	Facial rash (bilateral malar flush)	Possible reaction to NOLVADEX, treated with hydrocortisone.
		Carbohydrate intolerance	Diabetic exhibiting poor control.
		Nausea and vomiting	Possible reaction to NOLVADEX. NOLVADEX therapy interrupted, restarted for 3 days, then discontinued because of adverse events.
		Fever with neurological symptoms	
17	40	Anorexia	Due to NOLVADEX therapy.
19	20	Ataxia, weakness, itching, urinary incontinence, unsteadiness	Treatment with NOLVADEX and concomitant Megace.
21	40	None	

* Patients were treated in an adjuvant setting.

C. Summary of Responders

1. Case #2

A 53 year-old white male was diagnosed with right breast cancer in May 1974. He was initially treated with modified radical mastectomy. The ER was 23 fmol/mg protein and PR was 17 fmol/mg protein. The tumor recurred in the right axilla in May 1977. The patient had resection of the lesions followed by CMFP. The chemotherapy was stopped in April 1978 when he again recurred in his right axilla. Patient had no therapy until he was found to have new pulmonary nodules in October 1978. He was started on tamoxifen after refusing orchiectomy, adrenalectomy and hypophysectomy. Patient had therapy stopped after three days because of hypercalcemia. Symptoms resolved after 24 hours and therapy was resumed. X-ray report from 12/5/78 showed a reduction in the sizes of the pulmonary nodules. No measurements were done. On followup CXR on 1/3/79 there was again a decrease in size of nodular lesions in the lung. However, a new T-12 wedge lesion was noted, and T-7 wedging had worsened. Though the patient was declared to be a PR on the reduction of the pulmonary nodules, no mention was made of the new bony pathology. The duration of response was one month.

2. Case #3

A 73 year-old black male was seen at MDA in September 1977, three years after his initial diagnosis of breast cancer. He had no primary therapy in 1974 because of a multitude of medical problems. At MDA, he was found to have an unresectable ulcerated tumor plaque on his left anterior chest. The patient refused orchiectomy and was started on tamoxifen 10 mg BID in October 1977. Three months after starting therapy the soft tissue disease had resolved. In March 1978, patient had a 5 mm lesion of the left flank. No biopsy was obtained. Patient was taken off of study for multiple strokes in May 1978. Patient was considered to have achieved a PR of six months duration.

3. Case #4

An 88 year-old white male was diagnosed with cancer of his left breast in March 1975. He underwent a modified radical mastectomy. The ER was positive at 96 fmol/mg cytosol protein. The patient had a skin recurrence and underwent an orchiectomy in May 1976. He responded until February 1978 when he recurred in the skin. His estrogen receptor was positive at 468 fmol/mg protein. Tamoxifen was started on February 1978. Within one month, the patient had achieved complete response. His response lasted 7.3 months.

D. Summary of Dr. Ribeiro's Cases

Three cases out of twenty-four had a positive family history of breast cancer. Seven of the twenty-four patients had presented with metastatic disease. Fourteen patients had disease recurrence 8 to 60 months after initial diagnosis. The metastatic sites were bone, skin, lymph nodes, and lung. Sixteen patients had radiotherapy as adjuvant or for recurrent disease delivered before their tamoxifen therapy. Fifteen patients had mastectomies and two patients had lumpectomies as their primary surgical procedures. One patient had cytoxan therapy. One patient had an orchiectomy followed by tamoxifen therapy, and four patients received DES for their metastatic disease. Receptor statuses were available in 11 patients. Seven of 11 and 5/11 had positive ER and PR receptors, respectively. Although some patients started with a loading dose of 160 mg of tamoxifen, the daily dose was 20 mg/day.

Seven CR's and 2 PR's were reported; five patients had stable disease. The duration of responses reported ranged from days. Three of the responders had no prior therapy. One patient had pulmonary disease. One patient was ER/PR (-). Three patients developed a second primary during their followup: rectal, lung and prostate carcinomas. No toxicities were reported. (Table 3)

Table 3 Summary of Ribeiro's Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate)

Patient No.	Age	Race	Dominant Site	Prior Treatment	Receptor ER (fmol)	Receptor PgR (fmol)	Daily Dosage (mg)	Response Type[3]	Time to Response (days)	Duration of Response (days)	Duration of Treatment (days)	Site of Relapse	Second Primary	Comments
	77	White	Skin	None	206	431	20[1]	CR[4]	175	658	833	Skin Nodes	Carcinoma Rectum	Died 280 days after termination of therapy.
	65	White	Bone	None	256	120	20[1]	CR	139	1029	1168	Bone	None	Died 511 days after termination of therapy.
	61	White	Bone	Surgery Radiotherapy	Not done		20	PROG	—	—	301	Bone	None	Died 619 days after termination of therapy.
	53	White	Skin	Surgery Radiotherapy	0	0	20	PROG	—	—	56	Lung	None	Died 419 days after termination of therapy.
	64	White	Nodes	Surgery Radiotherapy	Not done		20	NC	—	204	204	Nodes	None	Died 704 days after termination of therapy.
	71	White	Nodes	Surgery	Not done		20	CR	774	1594	2368	—	Right Upper Lobe Bronchus	Alive 8040 days after termination of therapy.
	52	Black	Nodes	Surgery Radiotherapy	Not done		20[2]	CR	301	741	1042	None	None	Death - acute myocardial infarction while in complete remission/ disease absent.

[1] Day 1 - 160 mg.

[2] Reduced to 10 mg during treatment.

[3] CR = complete response
NC = no change
PROG = progression

[4] See text for details.

Table 3. Summary of Ribeiro's Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

Patient No.	Age	Race	Dominant Site	Prior Treatment	Receptor ER (fmol)	Receptor PgR (fmol)	Daily Dosage (mg)	Response Type[1]	Time to Response (days)	Duration of Response (days)	Duration of Treatment (days)	Site of Relapse	Second Primary	Comments
	63	White	Nodes	Radiotherapy	0	0	20	PROG	—	—	253	Bone	None	Died 516 days after termination of therapy.
	64	White	Skin	Surgery Radiotherapy DES	195	1800	20	PROG	—	—	259	Bone	Prostate	Died 793 days after termination of therapy.
	37	White	Skin Nodes	Surgery Radiotherapy DES	108	544	20	NC	—	114	114	Bone	None	Died 626 days after termination of therapy.
	74	White	Nodes	Surgery Radiotherapy	13	28	20	NC	—	595	595	Nodes	None	Died 222 days after termination of therapy.
	46	White	Bone	Surgery Chemotheray	0	0	20	PROG	—	—	112	Skin Nodes	None	Died 435 days after termination of therapy.
	81	White	Lung	Surgery	Not done		20	CR	294	693	987	Lung	None	Died 56 days after termination of therapy.
	76	White	Bone	Orchiectomy	Not done		20	PROG	—	—	89	Not stated	None	Died 234 days after termination of therapy.

[1] CR = complete response
NC = no change
PROG = progression

Table 3 Summary of Ribeiro's Case Report Forms - Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

Patient No.	Age	Race	Dominant Site	Prior Treatment	Receptor ER (fmol)	Receptor PgR (fmol)	Daily Dosage (mg)	Response Type[2]	Time to Response (days)	Duration of Response (days)	Duration of Treatment (days)	Site of Relapse	Second Primary	Comments
	86	White	Lung	Radiotherapy	Not done		20	PROG	—	—	81	Not stated	None	Died 56 days after termination of therapy.
	65	White	Skin Nodes	Surgery Radiotherapy	Not done		20	CR	56	749	805	Skin Nodes	None	Alive 147 days after termination of therapy.
	65	White	Lung	Radiotherapy	14	0	20	PROG	—	—	67	Not stated	None	Died 64 days after termination of therapy.
	50	White	Lung	Surgery Radiotherapy	Not done		20	NC	—	749	749	Lung Brain	None	Died 351 days after termination of therapy.
	44	Not Stated	Skin	Surgery Radiotherapy	Not done		20[1]	PR	311	201	512	Skin	None	Further treatment planned but details missing.
	67	Not Stated	Nodes	Surgery Radiotherapy DES	Not done		20	NC	—	239	288	Skin Nodes	None	Died 214 days after termination of therapy.
	74	White	Nodes	Surgery	Not done		30	PROG	—	—	215	Not stated	None	Died 661 days after termination of therapy.

[1] Day 1 - 160 mg.

[2] CR = complete response
NC = no change
PR = partial response
PROG = progression

Table 3 Summary of Ribeiro's Case Report Forms – Male Breast Cancer Patients with Advanced Disease Treated with NOLVADEX (Tamoxifen Citrate) (Contd)

Patient No.	Age	Race	Dominant Site	Prior Treatment	Receptor ER (fmol)	Receptor PgR (fmol)	Daily Dosage (mg)	Response Type[1]	Time to Response (days)	Duration of Response (days)	Duration of Treatment (days)	Site of Relapse	Second Primary	Comments
	42	White	Lung	Surgery Radiotherapy	Not done		20	PROG	—	—	61	Not stated	None	Died 594 days after termination of therapy.
	74	White	Skin Nodes	Surgery Radiotherapy Chemotherapy	0	0	20	CR[2]	200	144	344	Nodes	None	Died 566 days after termination of therapy.
	82	White	Bone	None	59	0	20	PR	99	647	746	Not stated	None	Died 290 days after termination of therapy.

1 CR = complete response
PR = partial response
PROG = progression

2 See text for details.

E. Summary of Responders

1. Patient

A 78 year-old male was started on tamoxifen 20 mg/day after biopsy proven stage III, ER (+) and PR (+) tumor of the right breast was diagnosed in May 1982. The patient was in CR by day 175. Therapy was terminated in August 1984 because of disease progression in skin and nodes. The duration of response was 22 months.

2. Patient

A 66 year-old white male with an ER and PR positive tumor of the left breast and metastases to bone and nodes was started on tamoxifen 20 mg/day in June 1981. The patient achieved CR by October 1981. He progressed in August 1984 in the bone. The duration of response was 34.3 months.

On review of the X ray reports submitted by ICI, CR was not achieved until 5/14/84. The subsequent X-ray report on 7/12/85 showed recurrence of his metastatic bone disease.

3. Patient

A 71 year-old white male was diagnosed with stage III cancer of the left breast in August 1975. He underwent a simple mastectomy. After a recurrence in his left axilla, he was started on tamoxifen 20 mg/day in August 1977. He achieved a CR by October of 1978 which lasted 80 months.

4. Patient

A 52 year-old black male with chronic schizophrenia and stage III breast cancer underwent mastectomy and radiation in 1975. He recurred in his left axilla in 1978. Tamoxifen was started in August 1978 and he achieved a CR by June 1979. Patient died of MI two years later still in complete remission.

5. Patient

An 81 year-old white male s/p mastectomy in 1972 for breast cancer was found to have pulmonary metastases in 1977. He was started on tamoxifen

in September 1977. His CXR was clear on August 1978. The patient recurred in July 1980 and was taken off therapy. The duration of response was 23.1 months.

6. Patient

A 65 year-old white male s/p mastectomy for stage I breast cancer in 1979, was found to have skin and left axilla recurrence in 1984. Two months after starting tamoxifen the patient was in CR. He recurred in his left axilla in April 1986 for a duration of 23.3 months.

7. Patient

A 44 year-old male who underwent local excision for stage I breast cancer in 1980 was found to have skin recurrence in March 1982. He achieved 50% reduction of his skin nodule in February 1983. The subsequent evaluation showed progression in August 1983. The duration was 6 months.

8. Patient

A 74 year-old white male who underwent a local excision for stage I ER and PR negative breast cancer in 1968 recurred in January 1976 in his left axilla and skin. He achieved complete remission in August 1976. However, he recurred in his left axilla in January 1977. The duration of response was 4.8 months.

9. Patient

An 82 year-old white male with breast cancer metastatic to bone was started on tamoxifen in October 1981. He had ER positive and PR negative tumor. After three months of therapy, the patient had 50% reduction of his breast mass and no new bone metastasis. However, no X-ray or bone scan were done to verify stable or improved skeletal disease. In October 1983 patient refused further therapy. Duration of response was 20.2 months.

F. Applicant's Conclusion:

"Overall, the information presented demonstrates that NOLVADEX has antitumor activity in male breast cancer and is clinically beneficial. It provides adequate evidence to support the claim that NOLVADEX is safe and

effective for the palliative and adjuvant treatment of male breast cancer."—

G. Reviewer's Comments:

The protocol stated that only patients that had failed conventional methods of treating breast cancer will be placed on this protocol. However, 5 patients (patients had no prior therapy. Patient had serious medical problems and probably could not undergo surgery, and refused orchiectomy. No reasons were given for the other patients.

Definitions of response are not provided to confirm uniformity in reporting. In addition, some patients had no data entry for greater than 6 months, making confirmation of PR or CR difficult. Because of the long duration over which information was obtained, the staging definitions, the technique for assaying estrogen receptor, and the surgical, radiotherapeutic and diagnostic procedures varied. However, most of the above will have little impact on the actual response of the patient to tamoxifen. Radiographic procedures used to detect and follow the disease would have an impact on the response determination. Measurable sites were followed with x-rays or bone scans because of the unavailability of CT and MRI scans.

Multiple deficiencies with the case report information makes validating a response difficult. The most troublesome issue is the duration a response had to be maintained. Below is a list of problems that have occurred in reviewing the case reports:

Goudsmit (ICI #2)

Tamoxifen was started on November 7, 1978. X-ray report from 1/3/79 stated that there was a decrease in size of nodular lesions in the lung. However, there was a new T-12 wedge lesion, and T-7 wedging had worsened. It is unclear when PR was declared and when the new bone lesions occurred.

Dr. Ribeiro' Cases —

13. (CR) Patient started therapy on 10/27/77. Pulmonary nodules were used to measure disease progression. CR achieved from 8/17/78 to 7/10/80. No X-ray reports or measurements available.

19. (PR) Patient started therapy on 3/30/82 with skin disease. PR achieved on 2/4/83; however, the next report in August '83 showed progression.

29. (CR) Patient started therapy on 1/24/76. Disease was located in left axilla and on skin. PR achieved by 6/16/76, and all disease resolved by 8/11/76. However, the next measurement in January '77 showed progression of disease.

The small number of patients and the lack of uniformity in them made it very difficult to merge this data and statistically present any meaningful survival data.

The lack of standard therapy for male breast cancer, current data available on the treatment of women, and CR's achieved with tamoxifen do support the use of this drug in metastatic male breast cancer. Historically, orchiectomy is the first treatment of choice; however, it is not a widely accepted form of therapy. Tamoxifen had less morbidity and most toxicities are reversible. Patients who fail or recur after orchiectomy may still respond to tamoxifen as seen in Case #4.

VI. The published literature on Advanced Breast Cancer

A. Summary of the Published Literature

One hundred and sixty-one patients with advanced breast cancer have been treated with tamoxifen in various phases of their therapy. The ages ranged from years. The dose of tamoxifen varied from mg/day. Twenty-three CR's and 20 PR's were seen; response rate fluctuated from %. Response durations varied from three to sixty months. The response rates and durations covered a wide range of numbers because of the small number of patients per report.

Dr. Ribeiro reported the largest series treated with tamoxifen (Ribeiro G: Tamoxifen (TAM) for the Treatment of Advanced Male Breast Cancer (MBC). Proc Am Soc Clin Oncol 7: 22, 1988). He treated 35 male patients with advanced breast cancer with 20 mg/day of Tamoxifen. Twenty-four of these cases were reported to ICI and were presented above. Including those 24 patients, 10 CR's and 4 PR's were reported with a mean duration of 27 months. Six patients had prior hormonal therapies. The mean age was 64 years and the mean

follow-up was 83 months. Responses were noted in soft tissue, bone and lung metastases. Five patients had stable disease for 15-62 months. Seventy-three percent of the patients with estrogen receptor positive tumor responded. No side effects were reported.

Patterson reported 17 additional patients treated with 20-40 mg/day of tamoxifen. The response rate was 47% with 5 CR's and 3 PR's (Patterson JS, Battersby LA, Bach BK: Use of Tamoxifen in Advanced Male Breast Cancer. Cancer Treat Rep 64(6-7):801-804, 1980). Twenty-four percent of the patients had stable disease.

Bezwoda had seven responders out of twelve patients (58%) (Bezwoda WR, Hesdorffer C, Dansey R, et al: Clinical features, hormone receptor status, and response to therapy. Cancer 60(6): 1337-1340, 1987).

Gartei reported 1 CR and 5 PR's in seven patients with male breast cancer (Gartei G: Tamoxifen (t) in elderly men with breast cancer (BC) (Abstract). Paper presented at the 14th International Cancer Congress, Budapest, 1986.) The reported toxicities included nausea (5/7), prurigo (1/7), and headache (1/7). The patient with the headache required dose reduction.

Other published case reports consisted of fewer patients with the response rates ranging between %. The overall response rate in evaluable patients was 53%.

Thirteen other patients were reported in the literature. Erlichman reported on ten patients treated in Canada; three had stable diseases and 7 progressed. (Erlichman C, Murphy KC, Elhakim T: Male Breast Cancer: A 13-Year Review of 89 Patients. JCO 2(8):903-909, 1984). Two patients were reported in letter form by Dr. Morgan. (Morgan DAL, Hong A: Carcinoma of the male breast and oestrogen metabolism. British Medical Journal July 15, 1978: 206). Neither patient responded to therapy. Dr. Jefferys reported on one patient with Klinefelter syndrome with bone metastases and a pleural effusion that achieved PR with tamoxifen. (Jefferys DB, Efthimiou J: Carcinoma of the male breast and oestrogen metabolism. British Medical Journal June 24 1978: 1697). (Table 4)

Table 4. Published Literature of Advanced Male Breast Cancer and TAM

	Country	no pt	id	age	ER	nodes	primary surg	adj xrt	adj chemo	horm adj	month rec	stage IV	refuse orch
Becher	Germany	1		43			Jul-78	Jul-78			thirty-one		1
		1		79			'63	'63			72		1
Bezwoda	Johannesburg	24											8 of 14
Digenis	USA												9 of 12
Ellision	USA	1		62	p	y						nodes, gi, lung	
Gartel	Italy	1		90	p	y	limited mastec						
		1		83	p	y							
		1		72		y							
		1		72		y							
		1		56	p	y							
		1		76	p	y	quadrantect						
		1		78	p								
Gomez	Mexico	1		64	n								
		1		64	n								
Gupta	USA	1		78	p	n	rm '66				60		
Hilliard	USA			58	p		mrm '76		CMF x 10		40		
Hortobagyi	USA	1		62								nodes, lung, bone	
Kantarjian	USA												
Lonning	Foreign	1		76									
Lopez	Italy	1		60							103		
		1		76								visceral	
		1		42							8		
		1		68							13		
		1		58							25		
		1		62							21		
		1		77							18		
Mercer	Australia	1			p						109		
					p						4		
					p						10		
					n						23		
					p						14		
					p						7		
					p							y	
Ouriel	128v2	1			n								
Okamoto	Japan	1		41	n							skin, lung	
Patel	USA	3											
Patterson	England	1		84								st	
		1										bone	
		1		55								st	
		1		66								bone	

Table 4. (Con't)

	Country	no pt	id	age	ER	nodes	primary surg	adj xrt	adj chemo	horm adj	month rec	stage IV	refuse orch
		1		48								liver	
		1		70									
		1		78								lung	
		1		79									
		1		58								lung	
		1											
		1		65								st	
		1		70								lung	
		1		83									
		1		80									
		1		72									
		1		77								st	
		1		88	p							st	
		1		53	p							lung	
Tirelli	Italy	1		64			m '70				70	lung, skin	
				44			m '75			orchiectomy	52		
				70			m '78				21		
				57		p							
Siddiqui	USA	1		66							96		
		1		66							56		
Erlichman	Canada	10											
Morgan	Nottingham	1		62			m				30		
		1		63			m				84		
Jefferys	England	1					rm '71				72		
Adami	Sweden												

Table 4. (Con't)

	#1	#2	#3	#4	dose	CR	PR	NC	PROG	Dur res	Toxicity	Survival
Becher	TAM				30		1					
	etradiol	cyproterone ac	TAM		30			1		54		
Bezwoda	2/6 orch	7/12 TAM	2/6DES		40		15/23			7		
Digenis												
Ellision	TAM				30		1					
Gartel	TAM				30		1				nausea 5/7	9
	TAM				30		1					12
	TAM				30						prurigo 1/7	
	TAM				30	1	1				HA 1/7	
	TAM				30		1					
	TAM				30		1					
Gomez	TAM + CMF											
	TAM						1					
Gupta	orchiectomy	chlorambucil	megace	TAM		1						
Hilliard	(orchiectomy)	TAM	(megace)						1			
Hortobagyi	orchiectomy	(CMF x2)	TAM		20		1			17		64
Kantarjian					20			1				
Lonning	(Dexamethasone)	Tam	arom inh	progestogens		2	3	3				
Lopez	(testolactone)	DES	CPA	TAM			1					
	(TAM)	HD MPA				1				40		135 +
	CPA	(TAM)	AG	EStradiol					1			15
	CPA	(TAM)							1			18
	TAM	AG							1			9
	CPA	TAM	(AG)	(HD-MPA)			1			9		23
	CPA	(TAM)				1				17		41 +
Mercer	TAM											6
	orchiectomy	TAM					1			23 +		
	(TAM)	orchiectomy					1			7 +		
	(TAM)	orchiectomy	chemotherapy									
	(orchiectomy)	(TAM)										
	(TAM)	DES										
	orchiectomy	TAM						1		35 +		
Ouriel	TAM					1				9		
Okamoto	TAM + chemo				60		1			30		
Patel	orchiectomy	adrenalectomy	TAM				3			mean 9		
Patterson	TAM				20		1			12 +		
	TAM						1					
	TAM				40	1						
	TAM				20	1				30		

Table 4. (Con't)

	#1	#2	#3	#4	dose	CR	PR	NC	PROG	Dur res	Toxicity	Survival
	TAM				40		1			12		
	TAM				20	1				3		
	TAM				40	1				20		
	TAM				40			1		18		
	TAM				20							
	TAM								1			
	TAM				40				1			
	TAM				20				1			
	TAM				40			1				
	TAM				40				1			
	TAM				40	1				4 +		
	TAM				20		1			6		
	TAM				20	1				7.5		
Tirelli	orchiectomy	(TAM)	(chemo)		20		1			1 +		
	TAM	chemo										
	(TAM)	orchiectomy			40			1		9		
	(TAM)	orchiectomy	chemo		40							
Siddiqui	estrogen	TAM										
	orchiectomy	TAM			20		1			18		128
Erlichman					20		1			84		194
Morgan	excision	(TAM)						3	7			
	(TAM)				40				1			
Jefferys	TAM								1			
Adami							1					

B. Reviewer's Comments:

The response rates reported are compatible with the response rates seen in treatment of estrogen receptor positive metastatic breast cancer in women. The response rate is less impressive in view of the small number of patients and the lack of definitions of complete and partial responses in the protocol . However, sixteen CR's were listed. The other problem with relying on reported literature is the lack of a true denominator because of the tendency of investigators to report only the positive cases and for only the positive cases to be published.

VII. Adjuvant Therapy

A. Case Reports

The NDA presented six male patients treated with tamoxifen 40 mg/day in the adjuvant setting. The ages ranged from years. All had stage II disease and were treated with modified radical mastectomy as primary surgical therapy. All had ER positive tumor. (Table 5)

Table 5. Summary of Case Report Forms - Male Breast Cancer Patients Treated with Nolvadex (Tamoxifen Citrate) in an Adjuvant Setting

ICI Case No.	Reporting Physician	Patient's Age (yr)	Previous Treatment	Receptor Status[1]	Mastectomy Type[2] (Positive Nodes/ Nodes Examined)	NOLVADEX Daily Dose (mg)	Duration of Treatment (days)	Adverse Events	Comments	Recurrence Site	Disease Free Survival (mo)
12	Dr. Arafah	61	None	ER+	Mod. Rad. (10/12)	40	994	None	After recurrence in Oct. 1982, patient treated with several drugs and died in Jan. 1985 of sepsis with widespread cancer.	Soft Tissue	32.7
13	Dr. Arafah	34	None	ER+	Mod. Rad. (3/20)	40	1,364	Decreased libido	Recurrence in Oct. 1983, then treated for bone metastasis. Lost to F/U in May, 1985.	Bone	44.8
14	Dr. Arafah	49	None	ER+	Mod. Rad. (4/19)	40	570	Decreased libido and impotence	Patient discontinued NOLVADEX because of adverse events on Jan. 6, 1982, but was free of disease. Lost to F/U as of 1-6-82.	N/A	18.1
18	Dr. Arafah	58	None	ER unknown	Mod. Rad. (7/15)	40	3,076+	Decreased libido and impotence	Patient continued on NOLVADEX at last F/U on 11/12/90 and was disease free.	N/A	101.1+
20	Dr. Arafah	70	None	ER+	Mod. Rad. (2/21)	40	1,493	Decreased libido and impotence	Patient refused therapy D/C because of adverse events with no evidence of disease.	N/A	49
22	Dr. Pearson	71	None	ER+ PR-	Mod. Rad. (6/unknown)	40	619*	None	Patient initially received NOLVADEX and 5-drug therapy (CMFVP) for 11 months. NOLVADEX then continued until 1/23/86 (recurrence).	Lung	20.4

1 ER = estrogen receptor
PR = progesterone receptor

2 Mod. Rad. = modified radical mastectomy

3 + = continuing treatment
* = also received 5-drug therapy (CMFVP)

Two out of six patients stopped treatment secondary to toxicity. They reported loss of libido and impotence. Two other patients had the same side effects but continued on therapy. Three patients had recurrent disease at 33, 45, and 20 months. One patient remains disease-free at 101+ months. (Table 6)

Table 6. Summary of Adverse Events - Male Breast Cancer Patients Treated with Nolvadex (Tamoxifen Citrate) in an Adjuvant Setting

ICI Case No.	Patient Age	NOLVADEX Daily Dose (mg)[1]	Duration of Treatment (days)[2]	Adverse Events	Comments
12	61	40	994	None	Disease-free survival for 32.7 months before recurrence was noted in soft tissue.
13	34	40	1,364	Decreased libido	Patient continued NOLVADEX therapy for 44.8 months after which bone recurrence was noted.
14	49	40	570	Decreased libido and impotence	Patient discontinued NOLVADEX Therapy after 18.7 months with no evidence of disease.
18	58	40	3,076†	Decreased libido and impotence	Patient continues on NOLVADEX therapy and is disease free after 101.1+ months
20	70	40	1,493	Decreased libido and impotence	After 49 months of treatment, patient refused further treatment because of adverse events and had no evidence of disease.
22	71	40*	619	None	Patient continued NOLVADEX therapy after 9 months of 5-drug concomitant therapy. Patient had a recurrence in lung after 20.4 months of NOLVADEX therapy.

(1) * Patient also received 5-drug therapy (CMFVP).
(2) † Indicate treatment continuing.

2 B. Published Reports

Dr. Ribeiro reported on 39 patients who had been treated with tamoxifen as adjuvant therapy (Ribeiro G, Swindell R: Adjuvant Tamoxifen for Male Breast Cancer (MBC). British Journal of Cancer 65: 252-254, 1992). They all had either stage II or stage III operable disease with positive axillary nodes. The therapy initially consisted of 20 mg tamoxifen for 1 year. Patients treated after 1988 received tamoxifen for two years. Seven patients recurred while on tamoxifen. Two patients did not complete treatment secondary to toxicities. The remaining thirty patients finished their prescribed course of therapy. Toxicities seen in adjuvant use of tamoxifen included alopecia, skin rash, decreased libido and impotence. No patients were lost to followup and the median followup period was 49 months. Thirty-one patients are currently alive. Eight patients had died; three died of nonmalignant diseases; and five died of breast cancer. Because of the paucity of patients, the patient data were pooled and compared to historical controls which consisted of 130 patients with Stage II or III disease treated between 1942 and 1975. An attempt was made to match the tamoxifen and control groups for age, stage, and type of tumor.

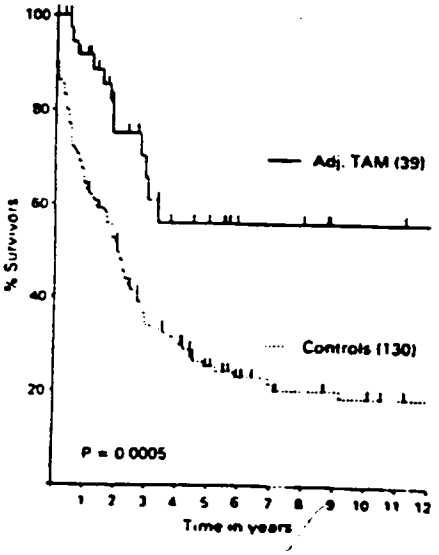


Figure 1 Disease free survival adjuvant TAM vs controls

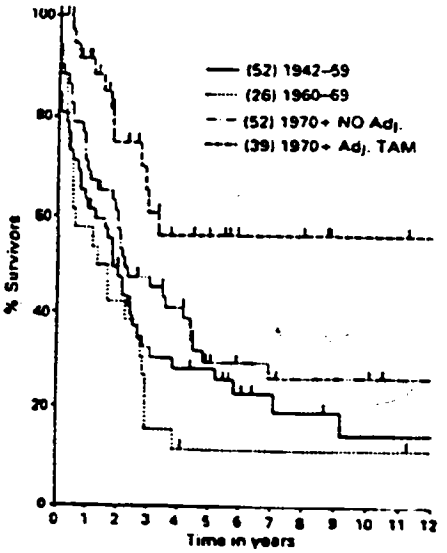


Figure 2 Disease free survival by year of treatment.

Figure 1 compares the disease-free survival of the two groups. Figure 2 shows the same information but splits the historical control groups by the year of treatment. The survival curves were calculated by the Kaplan-Meier method.

	5 Yr Disease-Free Survival	5Yr Act. Survival
Tamoxifen	56%	61%
Hist Cont	25%	44%
P value	0.0005	0.006

There were four other cases found in literature reported by three individual investigators. The patients had stages I - III disease. All were treated indefinitely. The duration of treatment ranged from + months. One patient died of colon cancer at 22 months. Two patients had adjuvant radiotherapy. No toxicities were reported. (Table 7)

Table 7
Adjuvant TAM

Name	No pt	age	stage	nodes	receptors	dose	duration	rec	mon rec	survival	toxicity	misc
Digenis	1		II					n		60 +		XRT +
	1		II	1				n		48 +		
Gomez	1		III		p			n		24+		XRT +
Siddiqui	1	72	I				22	n		22		died of colon ca

C. Reviewer's Comments:

The patient population is too small to draw any conclusion and the comparability of the historical control is questionable. Therapy may be too toxic for adjuvant therapy since one-third of the patients dropped out secondary to toxicity. The dose of tamoxifen in adjuvant therapy in female breast cancer is 20 mg/day; dropping the dose may decrease the toxicity and increase the compliance rate. Disease-free survival, survival and long term toxicity could not adequately be evaluated because of the small number of patients. Three patients out of the six patients reported were lost to follow-up. Dr. Ribeiro's report indicates some trend toward increased survival with the use of tamoxifen in the adjuvant setting. This application contains too few patients for adequate consideration of risk and benefit ratio in the adjuvant setting.

VIII. Recommended Regulatory Action

This supplemental NDA was presented to the ODAC on November 16, 1992. The committee recommended that the use of tamoxifen for metastatic breast cancer in males be approved. The reasons enumerated were there is an abundance of information available on metastatic female breast cancer from which we could infer response and toxicity data; the lack of serious toxicities seen in both male and female patients; the lack of effective standard therapy, and several complete responders were reported. On the other hand, there is insufficient data on adjuvant use of tamoxifen in male breast cancer, and the adjuvant use of tamoxifen in males is not approvable. Labeling deficiencies will be communicated to the applicant.

IX. Draft Labeling

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

NDA 17-970/S-024

/S/

A. P. Chen, M.D.

12/2/92

CC:
Orig. NDA 17-970/S-024
HFD-150/Div. File
HFD-150/A. P. Chen, M.D.
HFD-150/R. Justice, M.D.
HFD-150/J. Johnson, M.D.
HFD-150/P. Zimmerman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 17-970/S-024

PHARMACOLOGY REVIEW(S)

CC list complete FEB 1 8 1993

681

Division of Oncology and Pulmonary Drug Products
Pharmacology and Toxicology Review
Supplement 3

FEB 18 1993

NDA: 17-970 Supplement 024

Submission: NDA Dated: Feb. 1, 1993
Received by CDR: Feb. 4, 1993
Received by Reviewer: Feb. 16, 1993

Drug: Nolvadex (tamoxifen citrate)

Drug Supplier: ICI Pharmaceutical Company

Drug Formulation: Tablets contain 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg tamoxifen.

Pharmacologic Class: Hormones

Route of Administration: Oral

Indication: Male Breast Cancer

Subject: Fate of tamoxifen in rodents and comparison with human.

The biological response to tamoxifen and exogenous estrogens in male and female experimental animals and humans will be discussed in this review. This review is based on a literature search only. See supplements 1 and 2 of this series for more facts and speculations on tamoxifen (TAM).

TAM, triphenylethylene antiestrogen, has different pharmacological actions on various organs in different species of animals. This compound acts as an estrogen agonist/antagonist to the adult rat (J Reprod Fertil 13:101-119, 19670), as an estrogen agonist to the adult mouse (Acta Endocrinol 66:431-447, 1971), and a pure antagonist to the chick (Nature Lond 267:434-435, 1977). Thus the relative potency of TAM depends upon the animal exposure, the specific endpoint examined, and whether agonist or antagonist activities are measured.

Several studies suggest that the antiestrogenic action of the triphenylethylene class of compounds involves binding to the estrogen receptor at the estrogen binding site. Others propose that antiestrogenic action of triphenylethylenes may involve binding to an antiestrogen-binding site (Nature {Lond}288:273-275,1980; J Steroid Biochem 19:59-68,1983). However, despite numerous studies, the mechanism of the antiestrogenic action of tamoxifen and other triphenylethylene derivatives is still not fully understood.

Both male and female rats were equally affected by TAM during two year oral carcinogenicity study (IND
Positive dose-response relationships in liver hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular cholangiocellular carcinoma were observed in both male and female rats.

The LD50 values in different species under different experimental routs are given below.

Species	Sex	Route	LD50 mg/kg	mg/m2
Mice	M	iv	75 - 100	225 - 300
Mice	F	iv	62.5 - 75	187.5 - 225
Mice	M & F	oral	3,000	9,000
Rats	M	oral	2,750	16,500
Rats	F	oral	2,250	13,500
Rats	M & F	iv	50 - 62.5	300 - 375
Rabbits	M & F	iv	62.5	687.5

Similar toxic symptoms were shown by both male and female rodents during acute, subacute (3 months) and chronic (15 months) toxicity studies.

Conclusion: On the basis of the data presented above, there are evidence that male and female rodents exposed to TAM showed similar toxic responses at equivalent doses. It should be noted that rodents often demonstrate sex differences in response and pharmacokinetics not observed in human.

Clinical Support:

David Shewmon recently reported to AHA [Circulation, Sppl. 1, vol 86 (4) p 1345] that tamoxifen (10 mg twice a day for 3 months) can substantially lower lipoprotein(a) (25-50%) in **men** with severe coronary artery disease and initial LP(a) levels above 40 mg/dl. In addition, LP(a) levels were not observed to recover to baseline after 3 months off of tamoxifen. It has been reported previously that conjugated estrogen also lowered LP(a) levels in **women**.

FDA's Oncologic Drugs **Advisory Committee** recently recommended approval of Nolvadex for treating advanced metastatic breast cancer in men, but not for use as adjuvant therapy. Tamoxifen is approved for treating advanced breast cancer in women and as adjuvant therapy for breast cancer in women..

In response to FDA's approvable letter dated December 17, 1992, ICI Pharmaceuticals Group performed a literature search and did not find any differences in **pharmacokinetics and pharmacodynamics** between female and male cancer patients.

Recommendations: This NDA is approvable from the pharmacology/ toxicology point of view with the following change in the labelling.

(1) Sponsor should be asked to change the labelling under mutagenesis based on recent studies by Han and Liehr {Cancer Res. 52:1360-1363,1992} and White et al (Carcinogenesis 13:2197-2203, 1992) to state that tamoxifen is a genotoxic carcinogen.

This recommendation has been previously relayed and needs to be conveyed to the sponsor JJD

/S/

M. Anwar Goheer
February 18, 1993

cc:
Original NDA
HFD-150
/MAGoheer
/JJDeGeorge
/Medical Reviewer JJD 2/19/93
/CSO

DEC 3 1992

Record of Teleconference

Department of Health and Human Services
Food and Drug Administration
Division of Oncology And Pulmonary Drug Products

Date: December 4, 1992
To: File, NDA 17970 HFD 150

From: J. DeGeorge, Ph.D.
Supervisory Pharmacologist, HFD 150

With: T. Rogers, Regulatory Affairs ICI
Subject: Tamoxefin for treatment of Male Breast Cancer

I contacted Mr. Rogers to request that ICI do literature search and provide us with any information regarding differences sex differences in pharmacokinetics or pharmacokinetics in human or non-human species. Mr. Rogers indicated they would get back to us today with whether any information was available on this question.

Joseph J. DeGeorge 12/3/92
cc: HFD150 DeGeorge/ Justice/ Zimmerman
HFD 150 Drug file
HFD 150: RG Scully
Orig NDA 17970 - S/024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 17-970/S-024

BIOEQUIVALENCE REVIEW(S)

DF

MAR - 8 1993

Nolvadex 10 mg Tablet
(Tamoxifen Citrate)
NDA 17970 SE5(AF)024, Feb 15, 1993
Reviewer: Mehul U. Mehta, Ph.D.

Zeneca Inc.
Wilmington, Delaware
Submission Date:
February 17, 1993

Review of an Efficacy Supplement

BACKGROUND:

This efficacy supplement is for the male breast cancer indication. With regards to this indication, the sponsor has been asked by HFD-150 that "A literature search should be done to determine whether there are any differences in pharmacokinetics and pharmacodynamics between females and males.....If there are any significant differences, the information should be included in the labeling." The sponsor has responded by submitting twenty-eight abstracts and eight publications on tamoxifen. **It should be noted that the sponsor has not done any additional analyses besides submitting these publications and stating the following: "No changes were required to the labeling as no differences were seen."**

Drs. Burke and Justice requested Biopharm to review this submission in only a superficial manner with the opinion that this would require a detailed review only if gross differences were noted in tamoxifen PK between men and women.

COMMENTS:

1. Adam et al (Cancer Treat Rep, 64, 761, 1980) studied tamoxifen PK in 6 healthy male volunteers and noted that "After administration of a single dose of 20 mg, peak serum levels of tamoxifen were 42 ng/ml; those of the metabolite were 12 ng/ml. The half-lives of the drug and metabolite were approximately 4 and 9 days, respectively, after a single dose." The authors further note in their discussion section that "In female patients, it has been reported that peak levels of tamoxifen of 15 to 25 ng/ml were obtained after a single 10-mg dose and that a single dose of approximately 10 mg/m2 yielded a median concentration of 16 ng/ml. In both cases, elimination was slow. The peak tamoxifen levels achieved in the present study (35 to 45 ng/ml from a 20-mg dose) and the long terminal half-life agree with the above findings and suggest that no major pharmacokinetic difference exists in the handlig of tamoxifen between healthy male subjects and female patients with breast cancer."

2. The publication by Adam H.K. (Proc Symp NSABP, San Diego, May 22, 1981) has mean tamoxifen levels vs time plots for female patients and healthy males. Based on these data [see page 3 of this reivew] it appears that qualitatively, tamoxifen

disposition is similar between men and women.

3. publications by Guelen (Meth and Find Exptl Clin Pharmacol, 9, 685, 1987) and de Vos (same journal, 11, 647, 1989) provide tamoxifen PK parameters [AUC0-34, Cmax, Tmax] in healthy male volunteers following single dosing; unfortunately, these authors do not provide any comparison of these parameters with those obtained from females. Also, estimates of tamoxifen half-life from these studies, with blood sampling only upto 34 hours, are such that these data cannot be used to simulate steady-state tamoxifen levels in men which then can be compared with those reported in women.

RECOMMENDATIONS:

As stated in comments 1 and 2 of this review, information provided in the publications of Adam H.K. (1980, 1981) indicates that pharmacokinetic disposition of tamoxifen appears to be qualitatively similar between female patients and healthy males. This finding, coupled with the fact that tamoxifen is not a narrow therapeutic index drug [recommended dosing is 10 to 20 mg b.i.d.] indicates that changes in the pharmacokinetic section of the labeling for the males breast cancer indication are not warranted.

/S/ 3/8/93

Mehul U. Mehta, Ph.D.
Pharmacokinetic Evaluation Branch

MUM:mum:IBM PC:03/04/93

cc: HFD-150: NDA 17970
HFD-150: Div. File
HFD-150: Burke
HFD-150: Johnson
HFD-150: /MO/ Justice
HFD-150: /CSO/ Zimmerman
HFD-150: /Biopharm/ Mehta
HFD-420: Fleischer 3/9/93
HFD-426: Biopharm Drug File

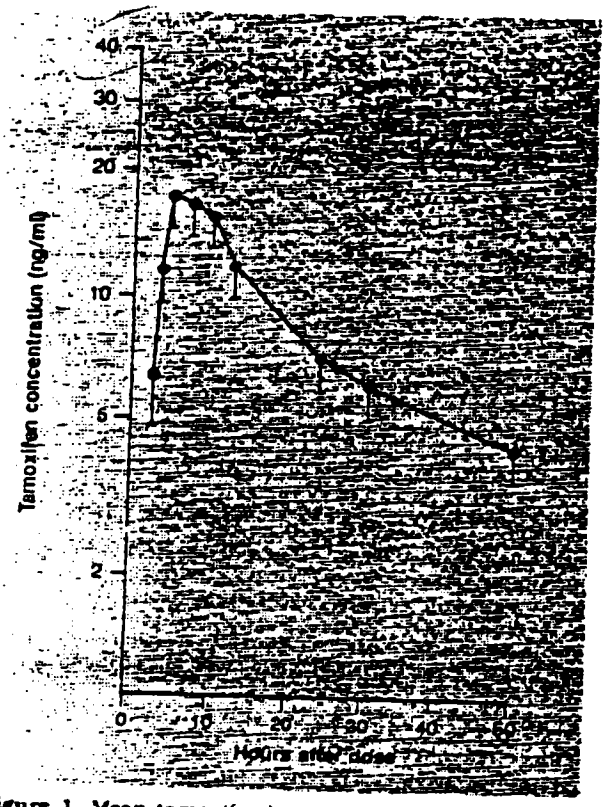


Figure 1. Mean tamoxifen levels in patients (n=6) after a single 10 mg dose of NOLVADEX®.

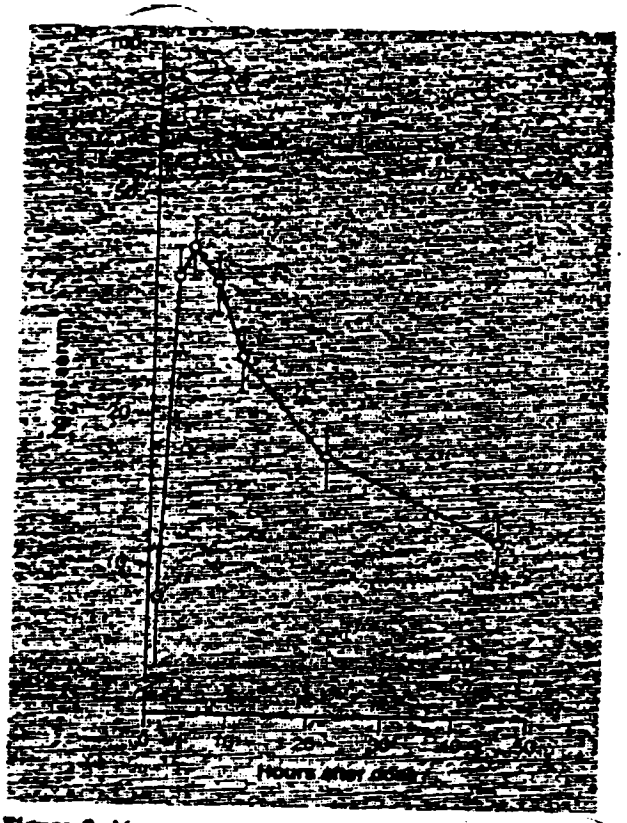


Figure 2. Mean tamoxifen concentrations in healthy male volunteers (n=6) after a single 20 mg dose of NOLVADEX (Profile to 48 hours).

The unchanged drug levels peak at around 18 ng/ml 3 hours after dosing. After the peak they decline fairly rapidly to 6 ng/ml by 30 hours. Figure 2 shows a similar study in healthy male volunteers given a single 10 mg oral dose.[8] Both these profiles fit with the data generated from ^{14}C tamoxifen citrate by Fromson, in that the apparent terminal half-life seems to be about 15 hours. However, if we follow the tamoxifen profile from our male volunteers for a longer period we can see (Figure 3) that there is a terminal half-life of 4 days in the elimination curve. That this is the true elimination half-life of tamoxifen was demonstrated by a study in 22 patients given 20 mg b.d. for 26 weeks.[9] Serum samples were obtained from these patients at various times over this period. The mean data (Figure 4) from this study clearly demonstrates that steady state values of tamoxifen are many times higher than those achieved by a single dose.

DF

Response to NDA Supplement Amendment 17970/S024 &S26

Date: March 19, 1993

The final labeling submitted by Zeneca on use of tamoxifen in male breast cancer, update information on incidence of endometrial carcinoma, and overdosage information is approvable with the following changes. Zeneca had agreed to the following changes (telecon 3/19/93).

Supplement S26 requested changes to the tamoxifen labeling updating incidence of endometrial carcinoma in NSABP B-14 trial. Nine patients treated on the tamoxifen arm had been diagnosed with endometrial carcinoma after 3-55 months on tamoxifen. Two patients recurred on the placebo arm and were been treated with tamoxifen for 28 and 45 months when they developed endometrial carcinoma.

In the same paragraph it states that 4,000 patients in other controlled studies showed no significant increase in the incidence of uterine cancer. This replaces a statement of review of 12,000 patients in twelve ongoing adjuvant studies that showed no increased incidence of cancer of the uterus. There is a discrepancy between the two statement of 5,000 patients. We addressed this question with Zeneca. They stated in their letter dated 3/17/93 that 4000 patients were based on three studies that specifically evaluated and reported on incidence of endometrial cancers.

Also, under the section of Overdosage, it listed toxicities seen on a phase I trial of high-dose tamoxifen. Neurotoxicity was the DLT and was seen at doses greater than 150 mg/m^2 BID. Also, prolongation of the QT interval on EKG was evident at doses greater or equal to 80 mg/m^2 BID. One sudden death occurred with cardiac arrhythmia. The labeling stated that "For a woman with a body surface of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 8 fold higher in respect to the maximum recommended dose." The dose of 80 mg/m^2 BID in a 1.5 m^2 woman is 6 times the maximum recommended dose of 40 mg BID.

In their last paragraph under Clinical Pharmacology, it states that" . . . clinical responses in 16 patients (13 evaluable) treated with Nolvadex.

I believe the above statement should read

The labeling stated that the safety profile in males is similar to that seen in women. In the literature and case reports of male patients treated with tamoxifen, patients terminated therapy secondary to loss of libido and impotence. Also, in the abstracts and articles on male patients with oligospermia treated with tamoxifen, increased levels of FSH, LH, estrogen and testosterone were measured. No clinical effects were detected

aside from varied responses in sperm morphology, sperm count and mobility in infertile males. These side effects should be included in the labeling.

Please make the following changes to the labeling at the next printing or within 3 months whichever comes first.

Recommendations:

1. We recommend including the names of the three trials (Scottish, Christie Hospital, and Danish trials) in the labeling to identify the 4,000 patients mentioned in the new paragraph on page 6:

/S/ 3/19/93
A. P. Chen, M.D.

/S/
M.D 3/19/93
Robert Justice, M.D.

CC:
NDA 17970\S24 & S26
HFD-150/DIV. FILE
HFD-150/A. P. Chen, M.D.
HFD-150/R. Justice, M.D.
HFD-151/P. Zimmerman
HFD-340