CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-109 (17-970/S-050)

Chemistry Review(s)

NDA 21-109

AP 1-24-02

Nolvadex®
(Tamoxifen citrate) tablets

AstraZeneca Pharmaceuticals LP

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Drug Products

(HFD-510)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-109

2. REVIEW #: 1

3. REVIEW DATE: 18-Jul-2002

4. REVIEWER: Yvonne Yang, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-Feb-2002
Amendment[1]	12-Apr-2002
Amendment[2]	17-Jul-2002

[1]Amendment provides for information for all establishments used in the manufacturing of this product.
[2]Amendment provides for cross-references for all DMFs used in the manufacturing of this product.

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca Pharmaceuticals LP
Address:	1800 Concord Pike, P.O. Box 8355 Wilmington, DE 19803-8355
Representative:	Laura Garcia-Davenport, MS Associate Director, Regulatory Affairs
Telephone:	302-886-7533

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Nolvadex®
b) Non-Proprietary Name (USAN): Tamoxifen citrate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- **Chem. Type:** 6
- **Submission Priority:** P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Developmental Disorders
[Treatment of McCune-Albright Syndrome]

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 and 20 mg tablets

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___X___ Rx _____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

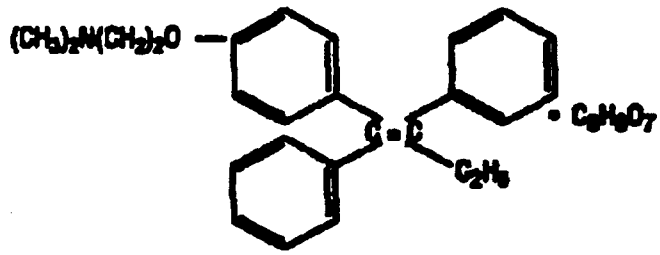
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Tamoxifen Citrate:

Chemical Name: (Z) 2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine : 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

Molecular Weight: 563.62 (citrate salt)

Chemical Formula: $C_{26}H_{29}NO \bullet C_6H_8NO_7$ ($C_{32}H_{37}NO_8$)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	1, 3	Adequate	Sept-08-86	1. Deficiency letter dated Jan-15-86 2. Amendment dated Feb-03-86
[redacted]	III	[redacted]	[redacted]	1	Adequate	Sept-6-1991	1. Deficiency letter dated Sept-12-91 2. Amendment dated Dec-10-91 3. Amendment dated Jan-06-93
[redacted]	III	[redacted]	[redacted]	1	Adequate	Apr-20-2001	Reviewed by Donald N. Klein
[redacted]	II	[redacted]	[redacted]	1	Adequate	Dec-11-2000	Reviewed by Yung-Ao Hsieh

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original	NDA 17-970	Nolvadex®

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Pediatric Exclusivity	Pending		Dragos Roman, M.D.
Biometrics	Acceptable		Todd Sahlroot, Ph.D.
EES	Overall OC Acceptable recommendation	May-03-2002	Yvonne Yang, Ph.D.
Pharm/Tox	Approval	Jun-27-2002	Wafa Harrouk, Ph.D.
Biopharm	Acceptable		Xiaoxiong Wei, M.D., Ph.D. Sang Chung, Ph.D.
LNC	Not needed		
Methods Validation	Methods previously validated for the approved strength		
OPDRA	Not needed		
EA	Categorical exclusion granted		Yvonne Yang, Ph.D.
Microbiology	Not needed		

The Chemistry Review for NDA 21-109

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-109 can be approved from the standpoint of chemistry, manufacture and controls.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Product:

Novaldex® (tamoxifen citrate tablets) are manufactured as immediate release uncoated tablets for oral administration. Nolvadex® was originally approved on Dec-30-1977 for the treatment and prevention of breast cancers. In the current application, the sponsor is seeking **pediatric exclusivity** for Nolvadex® for the treatment of McCune-Albright Syndrome in pediatric female patients. All information regarding chemistry, manufacture and controls of Nolvadex® are referenced to NDA 17-970 (in HFD-150).

Nolvadex® is available in the dose strengths of 10 mg and 20 mg tablets to deliver 10 mg and 20 mg of tamoxifen, respectively. Each 10 mg tablet contains 15.2 mg of tamoxifen citrate which is equivalent to 10 mg of tamoxifen. Each 20 mg tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen. The 10 mg Nolvadex® are packaged in bottles of 60, 180, and 2500 tablets. The 20 mg Nolvadex® are packaged in bottles of 30, 90, and 1250 tablets. Inactive ingredients in Nolvadex® include carboxymethylcellulose calcium, magnesium stearate, mannitol, and starch.

2. Drug Substance:

Tamoxifen citrate is a potent nonsteroidal estrogen antagonist. Tamoxifen citrate is known to have complex pharmacological properties, and can behave as a pure estrogen agonist, a partial agonist, or an antagonist, depending on the species of

animal, the target organ examined, and the endpoint measured. Tamoxifen citrate is known as a genotoxic carcinogen in the rat.

Tamoxifen citrate occurs as a fine, white to off-white, odorless, cryatalline powder. It is the trans-isomer of a triphenylethylene derivative. Relevant information regarding chemistry, manufacturing, and controls of the bulk drug substance are provided in DMF( ) and found adequate to support the original NDA 17-790 (in HFD-580) and the current NDA 21-109 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

B. Description of How the Drug Product is Intended to be Used

Nolvadex® should be dispensed in a well-closed, light-resistant container, and stored at controlled room temperature of 20-25°C (68-77 °F). The expiry for this product is 24 months. Novaldex® tablet should be swallowed whole with a drink of water with or without food at a daily dose of 20 mg.

It is noted that the sponsor only studied one dose (20 mg) for this new indication (see Clinical Pharmacology and Biopharmaceutics review dated Jul-02-02 for details). The optimal duration of Novaldex® therapy for the current indication has not been determined; and female children under the age of 2 years and older than 10 years of age should not take Novaldex® due to lack of studies on these populations (see Pharmacology/Toxicology review dated Jun-27-02 for details).

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-109 **can be approved** based on the following reasons:

(1) Nolvadex® is an approved drug product (NDA 17-970 in HFD-150) with no outstanding CMC issues (see chemistry consult review dated Jul-09-2002 for details).

(2) An overall acceptable recommendation is issued by OC on May-03-2002 (see attached EER report for details).

III. Administrative

A. Reviewer's Signature N/A

B. Endorsement Block N/A

C. CC Block N/A

Chemistry Assessment

A. Labeling & Package Insert

According to the applicant, the only part of the labeling that is affected by this new indication is the Package Insert. The proposed Package Insert was reviewed and found acceptable. All other parts of the labeling remain the same as what is currently approved for Novaldex® (NDA 17-970).

B. Environmental Assessment Or Claim Of Categorical Exclusion

This submission for Nolvadex® qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) as the concentration of the active ingredient, tamoxifen citrate, as calculated using the current and the previous submissions, at the point of entry into the aquatic environment, will be less than 1 ppb (amendment dated Apr-09-2002).

C. Establishment Inspection

An overall acceptable recommendation is issued by Office of Compliance on May-03-2002 (see attached EER report for details).

10-JUL-2002 FDA CDER EES Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21109/000
Org Code : 510
Priority : 6P

Sponsor: ASTRAZENECA
1800 CONCORD PIKE
WILMINGTON, DE 198038355

Stamp Date : 01-MAR-2002
PDUFA Date : 01-SEP-2002
Action Goal : 26-JUL-2002
District Goal: 03-JUL-2002

Brand Name : NOLVADEX (TAMOXIFEN CITRATE) TABS 20MG
Estab. Name:
Generic Name: TAMOXIFEN CITRATE TABLETS
Dosage Form: (TABLET)
Strength : 10 MG AND 20 MG

FDA Contacts: M. JOHNSON Project Manager (HFD-510)
Y. YANG Review Chemist (HFD-820) 301-827-6371
S. MARKOFSKY Team Leader (HFD-510) 301-827-6420

Overall Recommendation: ACCEPTABLE on 03-JUN-2002by S. FERGUSON(HFD-324) 301-827-0062

Establishment : CFN : 2517100 FEI : 2517100
ASTRAZENECA PHARMACEUTICALS LP
587 OLD BALTIMORE PIKE
NEWARK, DE 19702
DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-JUN-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-JUN-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610422 FEI : 3002850317
ASTRAZENECA UK LTD
BUSINESS PK CHARTER WAY, SK102NA
MACCLESFIELD, CHESHIRE, UK
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-APR-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASED ON PROFILE

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-APR-02		
Decision :	ACCEPTABLE		
Reason :	BASED ON FILE REVIEW		

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASED ON PROFILE

Establishment :

DMF No: AADA:

Responsibilities:

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-APR-02		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yvonne Yang
7/24/02 01:35:13 PM
CHEMIST

Sheldon Markofsky
7/24/02 02:40:43 PM
CHEMIST

Memorandum

To: NDA 21-109

CC: Yvonne Yang, Monica Johnson, HFD-510

From: Yung-Ao Hsieh, HFD-150

Date: 9-Jul-02

Re: NDA 21-109 Chemistry Consult Review

NDA 21-109 was submitted to HFD-510, on 1-Mar-02 providing for Nolvadex (tamoxifen citrate) 20 mg tablet for the treatment of girls with McCune-Albright Syndrome. Tamoxifen citrate is a nonsterodial antiestrogen. The drug product, available in 20 mg and 50 mg tablets, is approved for the treatment and prevention of breast cancers. There are no new CMC data provided in this pediatric application. The applicant refers to the approved NDA 17-970 for CMC information on tamoxifen citrate, USP drug substance and Nolvadex 20 mg tablets. A claim for categorical exclusion was filed in NDA 21-109 BC, dated 9-Apr-02.

Since Nolvadex 20 mg tablet is an approved drug and there are no pending CMC issues, approval is recommended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yung-Ao Hsieh
7/9/02 03:09:09 PM
CHEMIST

Rebecca Wood
7/9/02 03:36:22 PM
CHEMIST