CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 17-970/S-039 & S-040

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-150 DODP	17-970

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

Zeneca Pharmaceuticals
P.O. Box 15437
1800 Concord Pike
Wilmington, DE 19850-5437
Attention: W.J. Kennedy,
Vice President, Drug Regulatory Affairs
Tel: 302-886-2192

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATES(S)
SE1-040	30-Apr-98

6. NAME OF DRUG	7. NONPROPRIETARY NAME
NOLVADEX	tamoxifen citrate

8. SUPPLEMENT PROVIDES FOR:

a claim of categorical exclusion for environmental assessment to support the use of NOLVADEX for the prevention of breast cancer in women at high risk

9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
antineoplastic	RX X OTC ___	

13. DOSAGE FORM(S)	14. POTENCY
tablet	10 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS
CURRENT YES___ NO___
REVIEWED YES___ NO___

17. COMMENTS

See page 2

cc:
HFD-150/Div. File
HFD-150/RWood
HFD-150/YAHsieh
HFD-150/AChapman
R/D Init. by: RHW 9-15-98

18. CONCLUSIONS AND RECOMMENDATIONS

It is recommended that the request for a claim of categorical exclusion for an environmental assessment should be approved.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Yung-Ao Hsieh, Ph.D.	/S/	4-Sep-98

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Summary of the Application

NOLVADEX® (tamoxifen citrate) is currently approved as a second- line therapy for the axillary node-negative breast cancer in women. Based on data from the P1 Prevention Trial conducted by the National Surgical Breast and Bowel Project (NSABP), supplemental new drug application SE1-040 provides for the use of NOLVADEX® in the prevention of breast cancer in women at high risk. In support of this efficacy supplement, Zeneca submitted a claim of categorical exclusion.

The applicant reported that the expected level of tamoxifen introduced into the environment, as the result of the approval of this efficacy supplemental application and all previous approvals, will not exceed a concentration of 1 ppb into the aquatic environment. The applicant stated that to his knowledge, no extraordinary circumstances exist.

Conclusion and recommendation

Adequate information has been presented to show that the requested approval of the efficacy supplement NDA 17-970 SE1-040 qualifies for a categorical exclusion from the requirement to prepare an EA under 21 CFR 25.31(b). It is recommended that the claim for a categorical exclusion for an EA should be approved.

/S/

Yung-Mo Hsieh, Ph.D.
Review Chemist, HFD-150

/S/ 1-16-98

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

cc:
NDA 17-970
HFD-150/Div. File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/AChapman

CHEMIST'S REVIEW

1. ORGANIZATION: HFD-150 DODP

2. NDA NUMBER: 17-970 APR 29 1998

3. NAME AND ADDRESS OF APPLICANT (City and State)

Zeneca Pharmaceuticals
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437
Attention: Sandra L. Acquaviva
Manager, Marketed Products Group
Drug Regulatory Affairs Department
Tel: 302-886-2192

4. AF NUMBER:

5. SUPPLEMENT (S)

NUMBER(S)	DATES(S)
SE1-039	27-Jan-98

6. NAME OF DRUG: Nolvadex®

7. NONPROPRIETARY NAME: tamoxifen citrate

8. SUPPLEMENT PROVIDES FOR:

a claim of categorical exclusion for an Environmental Assessment to support the new indication (contralateral breast cancer)

9. AMENDMENTS DATES: BC , 7-Apr-98

10. PHARMACOLOGICAL CATEGORY: antineoplastic

11. HOW DISPENSED: RX X OTC ___

12. RELATED IND/NDA/DMF:

13. DOSAGE FORM(S): tablets

14. POTENCY: 10 mg and 20 mg

15. CHEMICAL NAME AND STRUCTURE:

16. RECORDS AND REPORTS
CURRENT YES ___ NO ___
REVIEWED YES ___ NO ___

17. COMMENTS

See page 2

cc:
NDA 17-970
HFD-150/Div. File
HFD-150/RWood
HFD-150/YAHsieh
HFD-150/AChapman
R/D Init. by: RHWood 9-29-98

18. CONCLUSIONS AND RECOMMENDATIONS

It is recommended that the request for a claim of categorical exclusion for an Environmental Assessment should be approved.

19. REVIEWER

NAME: Yung-Ao Hsieh, Ph.D.

SIGNATURE: /S/

DATE COMPLETED: 4-15-98

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mmary of the Application

vadex is currently approved in the US as a primary therapy for the palliative eatment of postmenopausal women with advanced breast cancer. Supplemental new drug application SE1-039 provides for literature-based data to support the use of Nolvadex in the reduction of contralateral breast cancer in patients receiving adjuvant Nolvadex therapy for breast cancer. However, no Environmental Assessment information was provided in the original filing. In response to the Agency's fax dated March 6 1998, requesting EA information, the firm submitted a claim of categorical exclusion for an Environmental Assessment in an amendment, dated April 7, 1998.

Zeneca reports the claimed indication for the reduction of contralateral breast cancer does not involve treating a new patient population; but is an additional benefit to a patient population already receiving Nolvadex therapy. The expected level of Nolvadex introduced, as the result of the approval of this efficacy supplemental application and all previous approvals, will not exceed a concentration of 1 ppb at the point of entry into the aquatic environment. The applicant stated that to his knowledge, no extraordinary circumstances exist.

Conclusion and recommendation

Adequate information has been presented to show that the requested approval of the efficacy supplement NDA 17-970 SE1-039 qualifies for a categorical exclusion from the requirement to prepare an EA under 21 CFR 25.31(b). It is recommended that the claim for a categorical exclusion for an EA should be approved.

/S/

Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

/S/ 4-29-98

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

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17-970
-150/Div. File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/PZimmerman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 17-970/S-039 & S-040

STATISTICAL REVIEW(S)

105.1 Ms chapman

Statistical Review and Evaluation

OCT 21 1998

NDA #:	17-970 Serial #: 039
Applicant:	Zeneca Pharmaceuticals
Name of Drug:	NOLVADEX
Indication:	Reduction of the occurrence of contralateral breast cancer in patients receiving adjuvant NOLVADEX therapy for breast cancer
Submission Date:	1/27/98
Medical Officer:	Karen Johnson, M.D.

Background

NOLVADEX was approved in the US for the indication of primary therapy for the palliative treatment of postmenopausal women with advanced breast cancer in 1977. Subsequently, several indications have been added to the label. This sNDA, based on literature review, proposes that NOLVADEX is indicated in the reduction of the occurrence of contralateral breast cancer in patients receiving adjuvant NOLVADEX therapy for breast cancer.

The statistical review will focus on the statistical methods used in the EBCTCG Overview. Statistical methods used in the three major trials (publications), NSABP B-14 trial, Stockholm trial and Scottish trials are acceptable. The details of the methods are described in the FDA medical officer's review.

Summary of EBCTCG Overview

Sixty three randomized controlled trials of adjuvant tamoxifen versus no adjuvant tamoxifen that began before 1990 were conducted involving a total of more than 42,000 women. Of the 63 trials, 55 were available for the analyses. The availability of data from these trials are summarized in the following reviewer's table.

Reviewer's Table 1. Data from the 55 Randomized Trials

Scheduled tamoxifen duration	Number of trials	Number of Women
1 year	14	9128
2 years	32	19212
~5 years	9	8349
Total	**55**	**36689**

Information about contralateral breast cancer (CBC) was available for about 88% of the tamoxifen-treated patients. Reductions of the occurrence of CBC are summarized in the following reviewer's table.

Reviewer's Table 2. Reductions in the incidence rate of contralateral breast cancer

Scheduled tamoxifen duration	Reduction	p-value
1 year	13%	NS
2 years	26%	.004
~ 5 years	47%	<.00001
Total	**30%**	**<.00001**

Reviewer's Comment: The reduction rates presented in the above table are lower than those presented in the FDA's medical officer's review. This is because the medical officer's review is based on the earlier results of the EBCTCG overview data where 40% data about CBC were missing. Estimates of the reduction rates based on the updated data are more reliable and are provided in the Reviewer's Table 2.

Meta-analysis was used to analyze the data from 55 randomized trials. Comparisons were based on the intent-to-treat principle. The method can be described briefly as follows. First, each trial was analyzed separately and the resulting chi-square test statistic was calculated. Second, the heterogeneity of the data from the different trials was tested using a chi-square test. Third, a weighted average of the treatment effect estimates obtained from the separate trials was used as an overall estimate of the effect.

Reviewer's Comment: Effects of tamoxifen on other type of tumors, including colorectal cancer, endometrial cancer and other than breast or endometrial cancer, were also evaluated in the overview. The p-values obtained should be adjusted for the multiple tumor types, for example, after adjusting for 4 different tumor types, p-value for testing the reduction in the incidence rate of contralateral breast cancer should be $p < .00004$ (Bonferroni method for Total). Due to a number of reported and unreported tests performed in this meta-analysis study, the overall false positive rate may be inflated.

Reviewer's Summary and Conclusions

The statistical methods used in the EBCTCG Overview are acceptable. The evidence provided in the EBCTCG Overview and other literature reports of major randomized clinical trials supports the sponsor's proposed new indication.

/S/

Alexandra Kapatou, Ph.D.
Mathematical Statistician

/S/

Gang Chen, Ph.D.
Mathematical Statistician

Concur: Dr. G. Chi Chi

CC:

NDA
~~IND#~~ 17-970
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HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Kapatou
HFD-710/ Chron

GCHEN/10/20/98 MSWORD - 'c:\fda.pro\review\N17970.rew'

This review consists of 3 pages of text.