Appendix E. Review of updated data

On October 16, 1998, we received a database with events diagnosed since the data lock date of 1/31/98. The data lock date for these events is March 31, 1998. The following table summarizes the total number of events diagnosed on NSABP P-1.

Table E1. Events as of 3/31/98 on NSABP P-1

Event	Sponsor		FDA	
	Placebo (n=6706)	Tamoxifen (n=6681)	Placebo (n=6706)	Tamoxifen (n=6681)
Invasive breast cancer	176	89	177	90
Non-invasive breast cancer[1]	68	35	NA	NA
DCIS[2]	NA	NA	43	26
Fractures[3]:				
Hip fractures	23	12		
Colles' fractures	23	15		
Other radial fractures	63	65		
Spine	30	23		
Deaths[4]	71	57		
Endometrial cancer[4]	15	36		
Other cancers[3]	98	98		
DVT[4]	22	35		
PE[4]	6	18		
Stroke[4]	24	38		
Cataracts[3]	507	574		
Cataract surgery[3,5]	73	114		

[1] Sponsor included DCIS and LCIS

[2] Pathology reports for all non-invasive breast cancers reviewed by DODP

[3] Primary data not reviewed for this endpoint

[4] Primary data not reviewed for cases reported after 1/31/98

[5] For women without cataracts at baseline

Invasive breast cancer

With the available follow-up, tamoxifen reduced the number of breast cancer cases by 49%. The following table summarizes the characteristics of the breast cancers as reported by the sponsor. The sponsor did not include information on the number of women with T4 lesions, sites of distant metastasis at presentation, or progesterone status of the tumors.

Table E2. Breast cancer characteristics, cases as of 3/31/98

Staging Parameter	Placebo	Tamoxifen	Total
Tumor size:			
T1	132	64	196
T2	34	21	55
T3	10	4	14
Nodal status:			
Negative	117	60	177
1-3 positive	36	14	50
≥ 4 positive	11	12	23
≥ 10 positive*	3*	3*	6
Unknown	12	3	15
ER status:			
Negative	30	38	68
Positive	132	41	173
Unknown	14	10	24

* These totals are included in the > 4 positive node category

Tamoxifen reduced the number of earlier stage breast cancers (smaller tumors; negative nodes or 1-3 positive nodes). In this update, the number of T3 lesions was decreased, although the number of events was small. Tamoxifen reduced the number of ER(+) tumors by 68% but had little effect on ER(-) tumors.

The sponsor supplied analyses of time to event for all breast cancers and for ER(-) cases.

Figure E1. Time to diagnosis of breast cancer

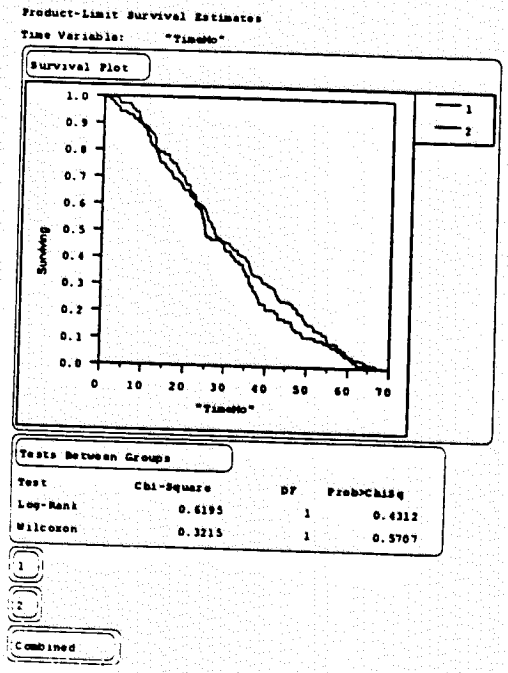
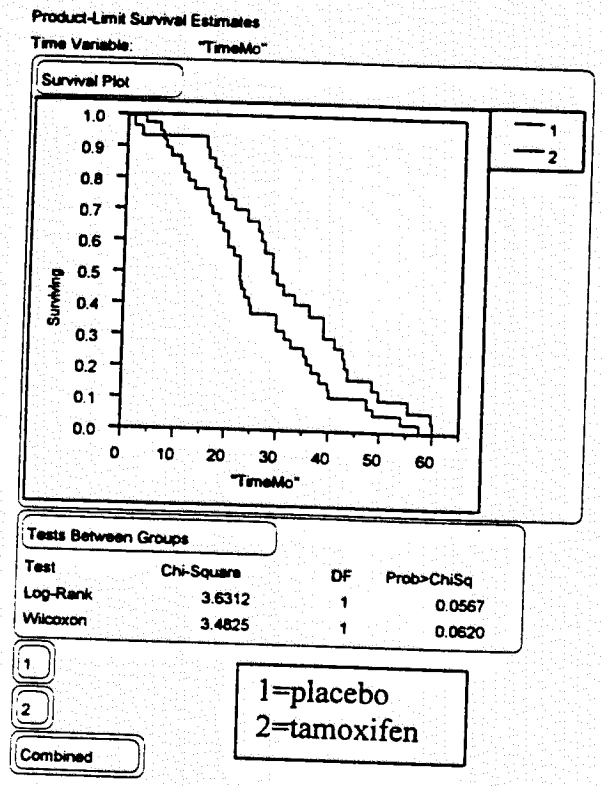


Figure E2. Time to diagnosis of ER(-) breast cancers



There was no difference in the time to diagnosis of all cancers or of ER(-) cancers between treatment arms.

Non-invasive breast cancer

Tamoxifen decreased the number of cases of DCIS by 40%. Fourteen new cases of non-invasive breast cancer were reported since 1/31/98, 10 on placebo and 4 on tamoxifen. Three of these cases were LCIS, 2 on placebo and 1 on tamoxifen. The case of LCIS on the tamoxifen arm was diagnosed in a woman with LCIS as part of her study entry criteria. Of the 2 women on placebo diagnosed with LCIS, 1 had LCIS as part of her study entry criteria. The reviewer has reported DCIS cases in the above table.

Fractures

The number of hip fractures is small, but the same trend towards a 48% reduction with tamoxifen therapy is observed. The number of Colles' fractures is not reliable, as there may be additional Colles' fractures included in the category "lower radial fractures." The number of wrist fractures (Colles' plus lower radial) is 86 on placebo and 80 on tamoxifen, not significantly different. Spine fractures were not a prospectively defined endpoint of the trial.

Adverse Events

The number of cases of DVT, PE, endometrial cancer, stroke, cataracts, and cataract surgery remain higher on tamoxifen than on placebo. The death rate is somewhat higher on placebo than on tamoxifen. There are no data available to address the possible source of this finding. The total number of other cancers and numbers of site-specific cancers were similar between the two treatment arms.

Summary

These data support the conclusions drawn from review of the original dataset.

Appendix F. Labeling review

See the attached labeling revisions

Appendix G. Recommended Action

The division recommends approval, with the following Phase IV commitments:

Phase IV Commitments

Medical Officer's Review of NDA 17-970
Ophthalmology Consultation

NDA # 17-970
Consultation

Submission: 9/10/98
Consult Request: 9/10/98
Review completed: 9/28/98

Name: Nolvadex (tamoxifen citrate tablets)

Sponsor: Zeneca Pharmaceuticals

Pharmacologic Category: Nonsteroidal with antiestrongenic properties

Proposed Indication(s): Prevention of breast cancer in women at high risk for developing the disease

Submitted:
1. Summary of Clinical Study: NSABP P-1, "A clinical trial to determine the worth of tamoxifen for preventing breast cancer.
2. Article from the Am J Ophthalmol 1998; 125:493-501.
3. Revised labeling proposal.

1. "Information was collected by asking patients at each visit about visual changes and ophthalmologic events. Evaluation of ophthalmic events on NSABP B-14 (tamoxifen versus placebo for estrogen receptor positive node negative breast cancer patients) suggested that tamoxifen administration might be associated with an increased incidence of cataracts. NSABP P-1 was designed to specifically examine this question in healthy women."

Reviewer's Comments:

It would have been more helpful to have examinations associated with the collection of the information concerning cataracts since cataracts cannot be self detected.

Relative risk of cataract and cataract surgery by baseline cataract status

Cataract Status at Baseline		Placebo	Tamoxifen	Rate Ratio	95% CI
Without cataracts at baseline	Randomized	6230	6199		
	Developed cataracts	483	540		
	Annual Rate	22.5	25.4	1.13	1.00-1.28
	Cataract Surgery	63	101		
	Annual Rate of Cataract Surgery	31.4	46.6	1.48	1.08-2.03
With cataracts at baseline	Randomized	477	482		
	Cataract Surgery	66	100		
	Annual Rate of Cataract Surgery	46.2	72.9	1.58	1.16-2.15

Reviewer's Comments:

There are multiple problems with the reporting of this information including the uniformity of the definition of cataract among patients, the method of detection (and the frequency of examination), type of cataract and the reason for cataract extraction. Even with these limitation, the finding of an increased rate of cataract extraction should not be ignored.

Information concerning potential risk factors was included, but the information was only recorded on a small subset of patients and is not helpful.

Other Ophthalmologic Events

Cases of Reported Vision Abnormalities were reported from individuals who experience eye problems during the course of the study.

Reviewer's Comments: *The information collected is not sufficiently detailed to permit conclusions of the type or frequency of events.*

2. Publication in the American Journal of Ophthalmology

Long-term Tamoxifen Citrate Use and Potential Ocular Toxicity

Methods: A single-masked, cross-sectional study involving multiple community and institutional ophthalmologic departments was conducted with a volunteer sample of 303 women with breast cancer currently taking part in a randomized clinical trial to determine the efficacy of tamoxifen (20 mg/day) in preventing recurrences.

Results: There were no cases of vision-threatening ocular toxicity among the tamoxifen-treated participants. Compared with non-treated participants, the tamoxifen-treated women had no difference in the activities of daily vision, visual acuity measurements, or other tests of visual function except for color screening. Intraretinal crystals (odds ratio [OR]=3.58, p=.178) and posterior subcapsular opacities (OR=4.03, p=.034) were more frequent in the tamoxifen-treated group.

Conclusions: Women should have a thorough baseline ophthalmic evaluation within the first year of initiating tamoxifen therapy and receive appropriate follow-up evaluations.

Reviewer's Comments:

1. *Clear differences were observed both in the color vision testing and in the frequency of posterior subcapsular cataracts.*

2. *Posterior subcapsular cataracts are the most common drug induced type of cataract.*

3. *Color vision testing would be expected to detect changes in visual function prior to changes in visual acuity.*

4. *The color vision abnormalities are of particular concern and suggest the need for follow-up on a six month schedule.*

3. Proposed Labeling

Reviewer's Comments: *The emphasis of the Warning as proposed is misleading. The non-significant finding should not be listed first (if at all in a Warning). The failure to detect a difference in visual disturbances is related to the methodology used to evaluate vision.*

Patient Information about NOLVADEX (tamoxifen citrate tablets)

Reviewer's Comments: *Recommended revisions to be consistent with recommended changes in package insert.*

Recommendations

It is recommended that the labeling be revised as identified in this review.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 17-970
HFD-150
HFD-150/Chapman
HFD-150/Honig
HFD-105
HFD-550/Consult File
HFD-550/Chambers

MEDICAL OFFICER'S CONSULTATION REPORT

SEP 3 1998

NDA 17-970, Serial No. S-040
DRUG: NOLVADEX™
GENERIC NAME: tamoxifen citrate
MANUFACTURER: Zeneca Pharmaceuticals
CONSULTATION INDICATION: Indication for Fracture Reduction

DATE OF REQUEST: August 25, 1998
DESIRED COMPLETION: ASAP
DATE REC'D., M.O.: August 27 , 1998
DATE COMPLETED: August 27, 1998

CONSULTATION REQUESTED BY:

Amy Chapman
HFD-150
Division of Oncology Drug Products

THROUGH:

Solomon Sobel, M.D., Director Division of Metabolic and Endocrine Drug Products, HFD-510
Gloria Troendle, M.D., Deputy Director; Team Leader, DMEDP; HFD-510
Enid Galliers, Chief Project Manager, DMEDP, HFD-510

Material Examined: 1) Reviewer's Comments on Label; 2) Label submission, pages 8-16; 3) Excerpts from Medical Review, cover page, pages 16, 45-49, 75-79.

RECOMMENDATIONS:

A. The data submitted are sufficient to warrant a *Safety* statement such as: *The NSABP Breast Cancer Prevention Trial (P-1) showed no increase in fractures of the hip, wrist, or spine with the use of Nolvadex up to 5 years.*

B. The fracture data are not sufficiently robust to permit a label statement concerning efficacy in prevention of fractures.

I. BACKGROUND

The proposed changes in labeling are based on one pivotal trial, NSABP P-1, a prospective multicenter randomized double-blind study of tamoxifen versus placebo administered for 5 years to women considered at high risk for breast cancer. The study randomized 13,388 women at 324 sites, grouped into 134 centers, in the United States and Canada.

The original objectives of the trial were to determine if tamoxifen:

- Decreases the incidence of breast cancer.
- Decreases the mortality from invasive breast cancer.
- Decreases the mortality from coronary heart disease.
- Decreases the occurrence of fatal and non-fatal MI.
- Influences the rate of fracture at various sites (both safety and efficacy issues).

No supportive data were submitted formally for review, although the original database, containing primary data, is available.

Hip and wrist were the primary fracture sites of interest because they could be documented with reliability and have high associated morbidity. Although information was collected on vertebral fractures (as well as on fractures at other sites), they were not to be included in analyses because many are asymptomatic and are difficult to diagnose reproducibly.

II. FRACTURE DATA

A. Proposed label, page 9: "There was a statistically significant difference in the number of hip fractures (9-Nolvadex, 20-placbo; RR=0.45, 55% reduction, 95% CI 0,21-0.99). For other protocol specified sites (wrist [Colles'] and spine), fewer bone fractures were seen in the Nolvadex group (7 and 31 cases) than in the placebo group (12 and 39 cases), respectively.

B. DODP Medical Review, page 75, Table 31: The same numbers appear, derived from the ERSMAC report, for these three fractures. The total number of fractures reported in the study were 533 in the placebo group and 518 in the Nolvadex group.
However, in the NSABP P-1 manuscript, the number of spine fractures was changed to 30 in the placebo arm and 19 in the tamoxifen arm, with no difference in the total number of fractures,

C. DODP Medical Review, page 76, Table 32: Annual hazard rates, taken from the NSABP P-1 manuscript, are shown. Using the same numbers, the 95% CI for hip fractures is listed here as 0.18-1.04. The DOCP reviewer has extracted additional data that revealed that some of the fractures occurred 1-4 years after discontinuation of the drug; recalculation of p5% CI has not been done after removing these. Since tamoxifen probably acts as an estrogen agonist on bone, it is appropriate to consider its action as similar to well-studied estrogens in prevention of fractures. Estrogens appear to exert fracture prevention action by virtue of inhibiting osteoclastic activity; this effect may persist up to 1 month after discontinuation of the agent and certainly cannot be expected to continue protection 1 year or more after discontinuation.

D. DODP Medical Review, page 78: When fractures are examined by age, using age 50 as the separation point, there is no significant difference in total fractures or the number of women with fractures between the two arms. There were more fractures in those over 50, as expected. There were fewer fractures of the wrist and hip in the tamoxifen arm in both age groups, but no statistics were calculated for each age group separately. Using the total numbers of fractures at each body site, the 95% CI included the value "1.00" and were therefor not significant at any site.

E. DODP Medical Review, page 79: The reviewer astutely lists several relevant observations:

- There were 84 and 78 radial head fractures, respectively, in the placebo and tamoxifen groups, which may have been overlooked Colles' fractures.
- Baseline records showed no differences in history of prior fractures, history of osteoporosis, history of past calcium use, history of current calcium use.
- Most fractures reported occurred in women without history of prior fracture or osteoporosis .
- No information was collected on use of drugs for osteoporosis.

III. CONSULTANT'S COMMENTS

C. The data submitted are sufficient to warrant a *Safety* statement such as: *The NSABP Breast Cancer Prevention Trial (P-1) showed no increase in fractures of the hip, wrist, or spine with the use of Nolvadex up to 5 years.*

D. The fracture data are not sufficiently robust to permit a label statement concerning efficacy in prevention of fractures.

1. The 95% CI for the relative risks of fractures in the prospectively designated areas (hip and wrist) include 1.00 (except in the unsubstantiated statement on page 9 of the submitted Draft Label).
2. Although the study was designed as a controlled protocol, it was not appropriate for a study of fractures.
   a. No baseline x-rays were obtained and thus the incidence of prevalent fractures is not known (this influences the rate of subsequent fractures).
   b. X-rays of incident fractures were obtained only after fracture was suspected on clinical grounds. Since the studies were conducted at 324 sites, variations in clinical practice may be expected unless protocols called for x-rays at specified times.
   c. Although baseline dietary calcium intakes were similar for the two groups, we are not told the levels reported. Furthermore, follow-up dietary surveys are needed, particularly in long-term studies and with the knowledge that some estrogens may affect general well-being and dietary intake.
   d. Since dietary vitamin D and its biologically activated form are significant factors in hip fracture, data concerning these are desirable.
   e. It would be helpful to have had surrogate endpoint data, such as are available for other estrogenic agents, including BMD (hip, wrist, whole body, spine); biochemical indices of bone formation (serum osteocalcin, bone specific alkaline phosphatase); biochemical indices of bone resorption (urinary N-telopeptide, deoxypyridinoline cross-links) to support the fracture observations.

/S/

Leo Lutwak, M.D., Ph.D.
Medical Officer
August 28, 1998

9-3-98

CC: NDA Archives
HFD-150/Div.Files
HFD-150/AChapman/DPease/SHonig
HFD-510/GTroendle/EGalliers/LLutwak

Medical Team Leader Review of Product Labeling

NDA 17-970, S-039
Drug: Nolvadex[R] (Tamoxifen Citrate)
Date of sNDA Submission: January 27, 1998

Materials Reviewed:

1) Revised product labeling submitted 6/24/98
2) Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: An overview of the randomised trials. Lancet 351:1451-1467, 1998.
3) Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, Costantino J, Redmond C, Fisher ER, Bowman DM, Deschenes L, Dimitrov NV, Margolese RG, Robidoux A, Shibata H, Terz J, Paterson AHG, Feldman MI, Farrar W, Evans J, and Lickley HL. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. JNCI 88:1529-1542, 1996.
4) Swedish Breast Cancer Cooperative Group. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. JNCI, 88:1543-1549, 1996.
5) Stewart HJ, Forrest AP, Everington D, McDonald CC, Dewar JA, Hawkins RA, Prescott RJ, and George WD. Randomized comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer. Br. J Cancer 74:297-299, 1996.
6) Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, and Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. JNCI 87:645-651, 1995.
7) Meeting Minutes, Pre-NDA Meeting with Zeneca Pharmaceuticals, 11/6/97.

Recommended Regulatory Action:

The submitted product labeling for Nolvadex[R] (Tamoxifen Citrate) accurately reflects the published results submitted in support of the proposed new indication, ***"Nolvadex reduces the occurrence of contralateral breast cancer in patients receiving adjuvant Nolvadex therapy for breast cancer. Current data from clinical trials support five years of adjuvant Nolvadex therapy for patients with breast cancer."***

The Division of Oncology Drug Products has agreed to accept a literature review, including the recently updated overview published by the Early Breast Cancer Trialists' Collaborative Group, in lieu of primary clinical data, since the results presented for the contralateral breast cancer indication are consistent with those already reported in product labeling for the adjuvant breast cancer indication.

In addition to the inclusion of information on contralateral breast cancer, the sponsor has updated language on the adjuvant use of tamoxifen in the **Clinical Studies** section, based on the publications above, as requested by FDA at the pre-NDA meeting. In particular, results for five versus more than five years of

tamoxifen use from the experience in NSABP B-14 and the Scottish Cancer Trials Breast Group has been incorporated.

The following issues regarding contralateral breast cancer were raised at the pre-NDA meeting, but are not addressed in current labeling:

1) The impact of contralateral breast cancer reduction on survival. This is difficult to assess since the benefits of a reduction in contralateral breast cancer appear to be offset, at least in some patients, by the occurrence of endometrial cancers. Thus, the benefit of tamoxifen use would be greater for hysterectomized patients than for non-hysterectomized patients.
2) Relative frequency of ER negative contralateral breast cancer with and without tamoxifen. This issue was not addressed in the published reports.

Supplemental NDA 17-970, S039, for Nolvadex^{R} (Tamoxifen Citrate) should be approved with the labeling revisions provided below.

/S/ 10/15/98

Julie Beitz, MD Date

cc:
HFD-150/ Division File
HFD-150/ J. Beitz
HFD-150/ S. Honig
HFD-150/ A. Chapman

MEDICAL OFFICER REVIEW OF NDA 17-970, S039

NOLVADEX^{R} CONTRALATERAL BREAST CANCER SUPPLEMENT

Table of Contents

1. General Information and Timeline

Drug name:	Tamoxifen
Applicant	Zeneca Pharmaceuticals
Submission date:	January 27, 1998
Pharmacologic Category:	Selective estrogen receptor modulator (SERM)
Proposed Indication:	"NOLVADEX is indicated in the reduction of the occurrence of contralateral breast cancer in patients receiving adjuvant NOLVADEX therapy for breast cancer."
45-Day Meeting:	March 18, 1998
Revised labeling submitted	June 24, 1998