2. Description of Clinical Data Sources

The submission consisted of 11 volumes which are described in the index to the application, pages 2 to 4, Volume 1. In the same volume, a draft package insert is provided as Item 2.A., pages 7 to 32. Volumes 1 and 6 through 8 were reviewed:

| Content | Volume |
|---|---|
| Application Summary and Proposed Labeling | 1 |
| Published Literature Reports | 7-8 |
| Integrated Summary of Effectiveness: | 6, Item 8.G. |

3. Introduction

At the end of 1977, NOLVADEX received marketing approval in the United States for the indication of "primary therapy for the palliative treatment of postmenopausal women with advanced breast cancer". Subsequently, several indications have been added to the label including the use of tamoxifen as 1) adjuvant therapy, 2) treatment for premenopausal women with advanced breast cancer, and 3) treatment for male breast cancer. In 1993, a proposed labeling change that claimed benefit from adjuvant tamoxifen relating to the reduction of contralateral breast cancer (CBC) was denied because a mechanism was not in place to review unverifiable data from the medical literature. In 1998, the issue is being revisited in light of draft guidance that permits a "literature-based" supplemental New Drug Application (sNDA). This sNDA proposes that "NOLVADEX$^{TM}$ (tamoxifen citrate) is indicated in the reduction of the occurrence of contralateral breast cancer in patients receiving adjuvant NOLVADEX therapy for breast cancer".

Contralateral breast cancer (CBC) can be defined as a diagnosis of invasive breast cancer in the second breast after simultaneous or prior diagnosis of breast cancer in the other breast. Such cases of bilateral breast cancer have been classified as 1) synchronous when tumors are diagnosed concurrently or close together in time vs. 2) metachronous when tumors are diagnosed at points separated in time by an interval that has been variously specified as 1, 3, 6, or 12 months. In the context of randomized clinical trials of adjuvant tamoxifen, no requirement is known to have been consistently imposed that CBC had to fit a specific definition of metachronous. A definition of CBC is not provided by the EBCTCG overview report. For individual trials, it would appear that when the first primary breast cancer was diagnosed, there was no evidence of a contralateral breast cancer and that adjuvant tamoxifen was started within a specified interval of time of the initial diagnosis. Some details may be gleaned from the individual literature reports for the various trials. For example, in the conduct of NSABP B-14, a patient could not have had a prior history of breast cancer and protocol treatment with tamoxifen or placebo was begun between 14 and 35 days after surgical removal of the primary tumor. Contralateral breast cancers were diagnosed within the first year of initiating protocol therapy, and the rate of CBC diagnosis was relatively constant over time, about 0.8% annually in the first and later years for patients in the placebo arm. CBCs were analyzed as a first event only.

Reviewer Comment: For the purpose of this sNDA, the sponsor and FDA reviewer have counted all CBCs reported as of the most recently published follow-up.

Preclinical evidence is available that supports the conclusion that anti-estrogenic interventions are associated with a reduced incidence of breast cancer. Before estrogen replacement became widely used in the 1970s, it was less likely for women undergoing ovariectomy to receive hormone replacement therapy with estrogen. In case control studies from that era, it was observed that women, whose ovarian function was prematurely ended, especially at younger ages (e.g. before the age of 35), subsequently experienced a reduction in the occurrence of primary breast cancer. In animal model systems of breast carcinogenesis, it was demonstrated that breast cancers could be reduced by ovariectomy. Breast cancer incidence reduction with ovariectomy in the laboratory as well as in case control studies is consistent with the laboratory observation that disruption of estrogenic action by an anti-estrogen such as tamoxifen can suppress the formation of mammary tumors in experimental animal models of breast carcinogenesis. Recently, data has been made available from the National Cancer Institute (NCI) that in 13,388 women without a breast cancer diagnosis but at a high risk of developing breast cancer who were enrolled in a randomized, double-blind, placebo-controlled trial and treated with tamoxifen, there was a 45% reduction in breast cancer incidence (Fisher et al., manuscript submitted for publication, 1998). The rationale for a breast cancer prevention trial with tamoxifen was largely based on an observed reduction in contralateral breast cancer in adjuvant trials of tamoxifen. Now the results from the NCI-sponsored prevention trial can be seen as being consistent with the thesis that adjuvant tamoxifen for breast cancer reduces the incidence of subsequent contralateral breast cancer.

Several lines of evidence have been used to support the conclusion that a diagnosis of contralateral breast cancer represents the occurrence of a new primary breast cancer in the breast opposite the one in which an original diagnosis of breast cancer has been made. One line of evidence is from pathology. It has been noted that contralateral breast cancers frequently include an *in situ* component (Cancer 1984; 15:3002-3011). It has been reasoned that *in situ* carcinoma is not consistent with the natural history of a metastatic lesion, but represents a lesion that is independent of prior disease, showing a transition from a precursor to a frankly invasive primary lesion. Another line of evidence that contralateral breast cancers are independent primary tumors has been provided by the analysis of "recurrence" events after an initial diagnosis of breast cancer. Broet *et al.* observed that following a diagnosis of breast cancer, unlike the risk of local or distant recurrence which decreased after 4 years of follow-up, the annual risk of developing a contralateral breast cancer remained constant well beyond 4 years post diagnosis (J Clin Oncol 1995; 13:1578-1583).

Reviewer Comment: This evidence supports the consideration of CBC reduction as an indication for adjuvant tamoxifen, that is distinct from its other benefits.

A comprehensive meta-analysis of randomized clinical trials (RCTs) of adjuvant tamoxifen from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was published in 1992 using data that was current through 1990. Of the 40 adjuvant trials comparing tamoxifen vs. the same without tamoxifen and analyzed by the EBCTCG for the 1992 overview, all were underway by 1984. There were 30,081 patients randomized to participate in these trials. Depending on trial size, duration of treatment, and results uncomplicated by the use of other adjuvant therapies, some of the 40 trials are more relevant than others in isolating the effect of adjuvant tamoxifen on the natural history of contralateral breast cancer. Only seven of 40 adjuvant trials planned for a duration of tamoxifen therapy of more

than two years and only 3 trials enrolled more than 1,000 patients: Stockholm B, Scottish, and NSABP B-14.

Of the three large (more than 1,000 patients) adjuvant tamoxifen trials, only the B-14 trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) was designed with a placebo arm such that participants and caregivers were uncertain as to whom was receiving tamoxifen. NSABP B-14 was the largest (starting with nearly 2,800 women) and after the initial 5 year treatment period proceeded into an extension phase comparing daily treatment with 20 mg of tamoxifen vs. placebo for a second 5 year period. Since all the patients in the B-14 trial had node-negative breast cancer, the potential for long term follow-up is greater than that for trials which included node-positive patients who were more likely to recur and die. A second major source of data is the Stockholm trial which randomized about 2,140 patients, but included node positive breast cancer patients (about 1/3). Data from the Stockholm trial differs from the NSABP B-14 trial and Scottish trial in several ways: 1) the daily dose of tamoxifen was 40 mg instead of 20 mg, 2) some women were also treated with CMF chemotherapy, and 3) the duration of use of tamoxifen was 2 years for most of the women randomized to tamoxifen, but a subset of about 400 women were re-randomized to continue tamoxifen for a total of 5 years. The Scottish trial enrolled just over 1,300 patients, who were randomized to receive adjuvant tamoxifen at a standard dose of 20 mg daily for 5 years vs. no tamoxifen until recurrence.

Reviewer Comment: NSABP B-14 is the richest single trial source of data for assessing the relationship between tamoxifen use and reduced contralateral breast cancer. The EBCTCG overview has combined the data from NSABP B-14 with 39 other RCTs examining the effect of tamoxifen on contralateral breast cancer. The overview process effectively salvages data from trials that are too small to have provided statistically meaningful results to address this question.

Of the 3 large trials with more than 1,000 patients enrolled, the results from NSABP B-14 and the Stockholm trial were sufficiently powered to compare the incidence of contralateral breast cancer in tamoxifen-treated patients vs. controls and show a statistically significant reduction of contralateral breast cancer in the tamoxifen group. In the 38 smaller trials, with patients often treated for durations of less than two years, an analysis for the effect of tamoxifen treatment on contralateral breast cancer is best examined in the context of a meta-analysis of all the trials. This review will concentrate on the results of the larger tamoxifen adjuvant trials and the EBCTCG overview as primary sources of data for an Integrated Summary of Efficacy of tamoxifen for the reduction in incidence of contralateral breast cancer.

Reviewer Comment: The statistical methods used in the EBCTCG overview and to analyze the data from the three large trials as described in the submitted literature will be assessed by the statistical reviewer.

4. Clinical Trials

NSABP B-14: The most recent update of the NSABP B-14 trial was published in November, 1996 (J Natl Cancer Inst 1996; 88:1529-1542). This trial was opened to accrual in 1982 with the goal of comparing tamoxifen with placebo as an adjuvant treatment for breast cancer patients after primary therapy when the tumor was found to be estrogen

receptor-positive and there was no evidence of axillary lymph node involvement with tumor. Participants in B-14 were randomized to receive 20 mg of tamoxifen p.o. daily vs. placebo pills of identical appearance for 5 years. Accrual to NSABP B-14 was closed in 1988 after 2,892 patients had been randomized. Approximately 2.6% of patients were found to be ineligible leaving 2,818 suitable for analysis (1,404 patients randomized to tamoxifen, 1,414 to placebo). Of the patients randomized to tamoxifen, 2.5% never started the protocol medication, and another 23% discontinued the drug during the first 5 years (11.2% for medical reasons). Of the patients randomized to placebo therapy, 1.6% failed to start the protocol medication, and another 23.5% discontinued the drug during the first 5 years (8.2% for medical reasons). For the second 5 year period of B-14, active treatment was not an option for 2,175 of the original 2,818 participants (due to, *e.g.*, initial treatment with placebo or an intervening event), but 643 did participate in a second randomization to continue with protocol therapy (322 randomized to tamoxifen, 321 to placebo). In the second 5 year treatment period, 1-2% of patients did not start the study medication and the percentage of patients who dropped out was on the order of 10 - 15%. For the patients who remained on study in the 2nd treatment period, compliance by pill count was estimated to be 94%.

Ten year follow-up results are available for the original 2,818 B-14 patients. The risk of having a recurrence event (local, regional or distant recurrence of breast cancer, contralateral breast cancer, second primary cancers, and deaths due to causes other than cancer) was reduced by 34% and the risk of death was reduced by 16%. The reduced risk of contralateral breast cancer was 37%. NSABP investigators concluded that there was no additional advantage obtained from continuing tamoxifen therapy for more than 5 years. The 5 and 10 year results for CBC are similar as shown by the following table:

**CONTRALATERAL BREAST CANCERS REPORTED FOR NSABP B-14**

| | No. of Cases | | Rates[1] | | |
|---|---|---|---|---|---|
| **Follow-up** | **Tamoxifen** | **Placebo** | **Tamoxifen** | **Placebo** | **Reduction** |
| 1st 5 years | 30 | 49 | 4.7 | 8.1 | 42% |
| 1st 10 years | 56 | 82 | 5.0 | 8.0* | 37% |

[1]Average annual rate per 1,000 patients

*For comparison of annual rates at 10 years, p = 0.007, 2-sided

Reviewer Comment: Given that the statistical analysis of the B-14 data was based on an intent-to-treat premise, it is probable that the reduction in the risk of developing contralateral breast cancer for patients who are able to be compliant is somewhat larger than the reported value of 37%.

A perspective on the relative importance of contralateral breast cancer as a recurrence event compared to 4 other breast cancer recurrence events (local/chest wall, ipsilateral breast, regional, distant) is provided by a comparison of the rates for these events in the placebo arm of B-14. In placebo-treated women, the 4 specified kinds of breast cancer recurrence are approximately 6 times more likely to occur than a contralateral breast cancer.

**Reviewer Comment**: The much greater risk of a recurrence of the previous primary compared to the occurrence of a new primary in the contralateral breast emphasizes the relevant importance of treatment benefits over CBC reduction benefits from the adjuvant use of tamoxifen in breast cancer patients. However, there are so many women using adjuvant tamoxifen as a treatment for breast cancer that on an absolute basis, a large number of women may be expected to benefit from the reduction of CBC.

In a second publication concerning the B-14 trial (J Natl Cancer Inst 1994; 86:527-537), the NSABP investigators estimated that the cumulative 5 year hazard rate of developing contralateral breast cancer during the first 5 years after surgery without adjuvant therapy was 4.05%, which was reduced to 2.35% with tamoxifen.

**Stockholm**: The most recent update of the Stockholm Trial was published in May, 1995. This publication focused on the issue of second primary malignancies (J Natl Cancer Inst 1995; 87:645-651). The Stockholm Trial was opened to accrual in 1976, with 2,729 patients accrued by the time of closure in 1990. Of the total patients in the Stockholm Trial, 1774 were defined as low risk (lymph nodes negative for tumor and primary less than or equal to 3 cm in diameter), and they were randomized to 40 mg of daily tamoxifen for 2 years vs. no additional treatment. The remaining 955 high risk patients had either a tumor that was greater than 3 cm in diameter or axillary lymph nodes that were involved with tumor. Of the 955 high risk women, 277 received axillary/chest wall irradiation only and 678 were randomized with half receiving tamoxifen in addition to either radiation or CMF chemotherapy, the others receiving radiation or chemotherapy without tamoxifen. Of the patients randomized to tamoxifen, 4% did not receive tamoxifen and another 10% discontinued tamoxifen before 2 years because of side effects including hot flushes and nausea. One percent of the control group received tamoxifen in spite of their assignment not to receive tamoxifen. Midway through accrual to the trial, a re-randomization was introduced so that patients who were free of disease after 2 years of tamoxifen would be randomized to stop tamoxifen or to continue it for an additional 3 years. There were 405 patients randomized for 5 years of tamoxifen therapy.

For the Stockholm Trial, contralateral breast cancers were reported whether they occurred before or after breast cancer recurrence. The number of patients with contralateral breast cancer was 40 in the tamoxifen group (totaling 1372) vs. 66 in the control group (totaling 1357). The risk of contralateral breast cancer was reduced 40% in the tamoxifen group, with an estimated 10 year cumulative incidence of 4.3% vs. 7.5% in the control group. The total number of breast cancer cases would have been slightly reduced from 40 to 36 in the tamoxifen group and from 66 to 59 in the control group if only contralateral breast cancer as a first event was counted as in the NSABP analyses.

## CONTRALATERAL BREAST CANCERS REPORTED FOR STOCKHOLM

| | No. of Cases | | Cumulative Incidence[1] | | |
|---|---|---|---|---|---|
| Follow-up | Tamoxifen | Placebo | Tamoxifen | Placebo | Reduction |
| At 10 years | 40 (36) | 66 (59) | 4.3 | 7.5 | 40%* |

[1]Estimated with actuarial (life-table) methods, patients at risk until new malignancy, death, or end date of follow-up
* Based on RR of 0.6, 95% CI= 0.4-0.9, p = 0.008

Scottish: The most recent information about CBC in the Scottish trial of adjuvant tamoxifen was published in July, 1987 (Lancet 1987; ii:171-175). From its beginning in 1978 to the close of accrual in 1984, 1,312 evaluable breast cancer patients after primary therapy for operable breast cancer were randomized to receive either 20 mg of tamoxifen daily, or no further treatment until the time of first relapse when tamoxifen was to be instituted. This trial was the first to have a planned duration of 5 years of treatment with adjuvant tamoxifen. In 1984, the trial was modified to allow a second randomization of patients taking tamoxifen for continuation of tamoxifen until the time of relapse vs. the discontinuation of tamoxifen at the end of 5 years. To be eligible for the Scottish trial, the patients were required to be <80 years old, with negative axillary nodes unless postmenopausal. Among the 1,070 postmenopausal women in the Scottish trial, 40% were known to have axillary nodes involved with tumor. Three percent of patients randomized to take tamoxifen were not treated either because they declined treatment or the prescriptions were not given. Tamoxifen was discontinued for toxicity in another 4% of patients, usually within a year of starting the medication. Another 1% of patients received tamoxifen in spite of being randomized to the observation group. Regardless of these inconsistencies, patients were analyzed as part of the assigned treatment group. The main outcome in this trial was that overall survival was extended by using tamoxifen in the adjuvant setting rather than waiting to use it at the time of recurrence. The increase in overall survival was due largely to a gain in relapse-free survival for the patients who received adjuvant tamoxifen. Although there were fewer cases of contralateral breast cancer in the group receiving adjuvant tamoxifen, the difference did not achieve statistical significance. There were 8 cases of CBC as the site of first relapse among the women in the adjuvant tamoxifen arm of the trial and 14 cases of CBC among the observed women. The absence of a statistically significant reduction in CBC in the Scottish trial is consistent with a lack of power to detect this endpoint.

Other Randomized Trials: For this submission, the sponsor has chosen to highlight results from 18 prospective randomized trials including the three large trials summarized above. The counts of contralateral breast cancers (CBC) for the 18 highlighted trials are enumerated in the Sponsor's Table 3, which is included for reference as Appendix II. Five of the trials (CRC, Danish, NATO, Christie/postmenopausal, South Sweden) were of sufficient size that there were more than 10 observed cases of CBC at the most recent report of follow-up; however, in only 1 of these 5 trials did the occurrence of CBC differ by more than 2 cases between the 2 arms. There are an additional 10 studies summarized in the table for which the total number of cases of CBC are less than 10.

Reviewer Comment: One of the 10 trials, the Christie (premenopausal) is inappropriate for inclusion in Appendix II and was not included in the EBCTCG meta-analysis. In the Christie (premenopausal) trial, premenopausal patients were randomized between 1 year of tamoxifen vs. an irradiation menopause. Since both of these interventions have an endocrine effect, and the comparison is not between tamoxifen and the same without tamoxifen, only the Christie (postmenopausal) study appears in the overview listing (Lancet 1992; 339:9).

The crude incidence of CBC, as reported in the table, is unadjusted for time on study. As the sponsor has noted, the effect of adding events across the various trials is to overlook disparities among the trials.

**Reviewer Comment**: The most appropriate way to assess the data in Appendix II is to conduct a formal meta-analysis such as that performed for the EBCTCG overview. Primary data from these trials was made available to the EBCTCG, and procedures were followed to adjust for differences among the trials in patient survival and other dimensions.

The sponsor has isolated the data from Appendix II that applies strictly to postmenopausal women. The crude incidence of CBC in tamoxifen-treated patients was 2.2% of 3,697 postmenopausal women compared with 3.6% of 3,681patients in the control group, for a 39% reduction. A similar approach has been used for node-negative patients with similar results. The crude incidence of CBC in tamoxifen-treated patients was 3.7% of 1670 node negative women compared with 5.7% of 1,681 node-negative controls for a 36% reduction. For node-positive patients, the crude incidence of CBC in tamoxifen-treated patients was 1.3% of 1,118 compared with 2.3% of 1,118 node-positive controls for a 46% reduction.

**Reviewer Comment**: It appears that the reduction in CBC for women specified as being postmenopausal or node negative is entirely consistent with the reduction observed for the larger population of women treated with tamoxifen in RCTs. The reduction in CBC for node positive patients is similar, but less data is available and the counts of CBC in these women are lower probably because they were more likely to experience recurrence of their primary tumor and death.

The sponsor reports that the crude incidence of CBC in 505 women identified as being premenopausal was 1.8% compared with 1.9% in 482 premenopausal control women.

**Reviewer Comment**: This amount of CBC data for premenopausal women is too sparse to be used for meaningful conclusions. Although it is an extrapolation to compare women who have never had breast cancer with breast cancer patients in adjuvant trials, results from the Breast Cancer Prevention Trial would suggest that with tamoxifen treatment, the reduction of CBC in premenopausal women is comparable to the reduction seen in postmenopausal women.

**Unrandomized Retrospective Studies**: The sponsor has described the published results of 5 retrospective "trials". Only one report out of the 5 was based on information from clinical trials; however, the **MD Anderson** clinical trials (not strictly concurrent) summarized in that one article included no information from a randomized comparison of patients who received tamoxifen vs. those who did not {Am J Clin Oncol (CCT) 1988; 11:114-118}. In 4 MD Anderson trials, 1,036 patients with operable breast cancer were treated with adjuvant therapy. In the first two of these trials, no one received tamoxifen. In the last 2 of these trials, women who were estrogen receptor positive and some with unknown receptor status were treated with tamoxifen. Consequently, of 17 patients who developed contralateral breast cancer during or after completion of adjuvant therapy, only 3 received tamoxifen and their comparison with the other 13 patients is biased by treatment selection factors and cohort effects. The "**Aukland** Contralateral Breast Cancer Detection Study" was not a trial, but rather a descriptive assessment of a case series, consisting of 2,706 patients who were diagnosed with breast cancer in Auckland between September, 1976 and September, 1985 (NZ Med J 1993; 106:23-25). Patients with metastases at presentation were dropped from the assessment (305). Among 374 patients who were identified as receiving endocrine therapy, 4 developed contralateral breast cancer (1.1%). Among 1,980 patients who were identified as not having endocrine therapy, there were 57 contralateral breast cancers (2.9%).

These results were biased by the selection factors that determined tamoxifen use and were not adjusted for the length of follow-up. Another publication has described a second case series from the **Institute Curie**, Paris (J Clin Oncol 1995; 13:1578-1583). At this institution, 4,748 patients with stage I to IIIa breast cancer were accessioned between 1981 and 1987. Of these patients, 441 received adjuvant hormonal therapy, 669 received adjuvant chemotherapy, and 3,638 received no adjuvant therapy. This data set was subjected to a sophisticated set of analytical procedures, but to address the question of contralateral breast cancer in women who had used adjuvant tamoxifen compared with those who had not, the authors of the paper appropriately concluded that statistical power was not sufficient. A third case series from 2 hospitals in **Uruguay** has been described in the literature, but is not informative for this review (Int J Radiation Oncology Biol Phys 1995; 31:765-775). This article provides results for 796 breast cancer patients who were treated with breast-conserving surgery followed by radiation therapy for early breast cancer. It is reported that 67 patients had CBC; however 13 of these patients were picked up in the series at the time that the second breast became involved with cancer, and 12 patients had concurrent bilateral breast cancer. Out of 42 remaining patients described as having "consecutive" bilateral breast cancer, 16 of the 42 were reported to have either 1) inflammatory inoperable cancer or 2) "bilateral cancer and antecedent or simultaneous distant metastases". The article does not specify how many of the 16 had bilateral disease, but inclusion of these patients in an analysis of the effect of tamoxifen on 2nd tumors does not make sense. Insufficient data is provided by the article for it to be useful to this review. A fifth report in this set of retrospective studies describes a case-control study nested within a population-based registry for the NCI's Surveillance, Epidemiology and End Results (SEER) program (J Natl Cancer Inst 1995; 87:1359-1364). From a cohort of 12,598 breast cancer cases (all in women < 85 years of age, stage I, II, or III, unilateral, diagnosed from 1/1/78 to 12/31/90) in the western portion of **Washington** state, there were 234 cases of contralateral breast cancer. Treatment with tamoxifen was associated with a decreased risk of CBC {odds ratio (OR) of 0.5, 95% CI = 0.3-0.9}. The OR was slightly less, 0.4, if tamoxifen had been used for more than 1 year or if the patient was postmenopausal at the time of breast cancer diagnosis. The mean duration of tamoxifen use was 21-22 months and the median time between first and second primary breast cancer was 39 months.

**Reviewer Comment**: Given the biases inherent to retrospective studies and the absence of randomization which controls for bias and confounding, even though there are some interesting results from some of the 5 retrospective studies mentioned above, the quality of the evidence from these studies has little if any role to play in this review.

5. **1992 EBCTCG Overview**

Using the EBCTCG overview methodology, the undue emphasis of favorable or unfavorable trial results is moderated by a systematic analysis which includes data from every known RCT conforming to a treatment issue such as the reduction of CBC in breast cancer patients treated with tamoxifen.

**Reviewer Comment**: If the results from the NSABP B-14 trial and the Stockholm trial are to be seen as reliable indicators that treatment with tamoxifen reduces the risk of developing contralateral breast cancer, then it is important that the results from these two individual trials are incorporated in and found to be consistent with the 1992 overview results for the aggregate 30,000 women in randomized clinical trials of adjuvant tamoxifen.

Supported by worldwide collaboration, the overview process collects and checks data from any formally randomized clinical trial of systemic adjuvant therapy for early breast cancer that started before 1985. Data acquisition on a worldwide basis appears to have been feasible except that no results are available for trials conducted in Russia. Although some of the RCTs in the overview compared adjuvant tamoxifen alone vs. placebo or no other therapy, others compared tamoxifen or no tamoxifen in combination with other approaches including chemotherapy, immunotherapy, or ovariectomy. For the overview, information was combined in such a way that it was not assumed that the patients in one trial were comparable to those in the others. The indirect comparison of randomized outcomes was accomplished by analyzing overall survival and recurrence-free survival with a logrank test of the difference between the observed vs. expected outcome with its variance.

The main results from the EBCTCG overview of adjuvant tamoxifen are included in the following table:

**SIGNIFICANT REDUCTIONS IN EVENT RATES ASSOCIATED WITH ADJUVANT TAMOXIFEN AS REPORTED BY EBCTCG**

| Outcome | Events / pts | | Events | | Reduction | |
|---|---|---|---|---|---|---|
| | Tam group | Control group | Observed -Expected | Variance of O-E | | |
| CBC | 122/9128 | 184/9135 | -37.2 | 74.6 | 39% SD 9 | (1p<0.00001) |
| Recurrence | 5052/15027 | 6043/15054 | -695.2 | 2416.1 | 25% SD 2 | (2p<0.00001) |
| Mortality | 3852/15027 | 4387/15054 | -341.5 | 1891.5 | 17% SD 2 | (2p<0.00001) |

For these summary results, the median duration of tamoxifen use was 2 years. Longer-term use of tamoxifen was generally found to be more effective than short exposure for any of the 3 endpoints in the preceding table; however, for the reduction of CBC, only a non-significant trend toward a larger effect with longer periods of treatment could be observed:

**NON-SIGNIFICANT TREND OF EFFECT WITH LONGER DURATIONS OF TAMOXIFEN USE**

| Years of Use | CBC Reduction |
|---|---|
| <2 years | 26% SD 21 |
| 2 years | 37% SD13 |
| >2 years | 53% SD 16 |

The data from the overview about contralateral breast cancer after randomization but before death was based on a smaller data set than that for the recurrence and mortality endpoints. Information about contralateral breast cancer was available for only about 60% of the tamoxifen-treated patients. No information is given in the overview publication as to the factors that contributed to the absence of contralateral data. The EBCTCG overview also did not comment on whether CBC reduction varied by subsets based on age and menopausal status.

Reviewer Comment: Missing data about contralateral breast cancer in about 40% of the 30,000 patients in adjuvant tamoxifen trials raises the possibility that CBC reduction may be somewhat different for the 12,000 patients for whom CBC data is not available. An updated report of the EBCTCG meta-analysis is expected later this year and may address some of the information gaps present in the 1992 report.

6. Integrated Summary of Efficacy

The EBCTCG overview provides an integrated summary of efficacy, estimating that in breast cancer patients treated with adjuvant tamoxifen, there is a 39% reduction in the risk of developing CBC. This result is based on data for 9,128 women randomized to treatment with adjuvant tamoxifen compared with 9,135 controls. The value of CBC reduction reported for the overview data is very similar to the statistically significant reduction of 37% reported for NSABP B-14 for which the follow-up is more complete. Reductions in CBC reported for the Stockholm and Scottish trials are also consistent with the overview. In the many smaller trials that had insufficient CBC events to be adequately powered for a statistically significant independent result, the aggregated data supports a claim of CBC reduction on the basis of its contribution to the EBCTCG overview. The consistency of all these results is one aspect of the evidence that strongly supports a reduction in CBC by tamoxifen. Other aspects of the evidence that support this claim are the biologic plausibility of the result, the time course of the effect, and the gradient that suggests that longer durations of exposure up to 5 years are consistent with greater reductions in CBC. Information has not been provided that allows for an assessment of benefit from CBC reduction with durations of tamoxifen use longer than 5 years.

7. Integrated Summary of Safety

An "Integrated Summary of Safety Information" is not a major focus of this sNDA in keeping with the thesis of the draft guidance, "FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products", that new supplemental indications for approved drugs can be streamlined. In the context of adjuvant therapy, the safety of tamoxifen has been previously reviewed and is well established; consequently, the safety considerations relevant to the indication of adjuvant tamoxifen for reduction in the incidence of contralateral breast cancer are identical to those provided by prior submissions for tamoxifen as an adjuvant therapy. Since the claim for a tamoxifen-related reduction in contralateral breast cancer is based on the standard dose and schedule already described in the product label, the safety/toxicity information in the label is an acceptable and appropriate summary of safety information for the indication under consideration.

As part of this sNDA, it has been proposed that the label be revised in its description of product toxicity with respect to thrombotic events. The information to be added to the label was published in November, 1996 (J Natl Cancer Inst 1996; 88:1529-1542). In addition to hot flushes and vaginal discharge, a third adverse experience was observed to occur in excess for tamoxifen-treated patients compared to placebo-treated paitients. The published report indicates that through 5 years post randomization, venous thromboembolic events occurred in 0.4% of placebo-treated patients compared with 1.7% of tamoxifen-treated patients. The following breakdown was given in the publication:

**THROMBOEMBOLIC EVENTS REPORTED FOR NSABP B-14**
(J Natl Cancer Inst 1996; 88:1536

| Adverse Events | With tamoxifen | With placebo |
|---|---|---|
| Superficial Phlebitis | 0.4 | 0.0 |
| Deep Vein Thrombosis | 0.3* | 0.1* |
| Pulmonary Embolism | 0.4* | 0.2 |
| Requiring Hospitalization | 0.5 | 0.1 |
| Death | 0.1 | 0.0 |
| | | |
| Total Thromboembolic events | 1.7 | 0.4 |

*Proposed labeling differs slightly on these values.

8. Sponsor's Conclusions

The sponsor's conclusions have been provided as follows:

> *"The beneficial effects of tamoxifen to reduce the occurrence of new primary breast cancers in the opposite (contralateral) breast have been demonstrated in a substantial number of independent clinical trials. Currently, tamoxifen is the only hormonal agent shown to produce this effect in the adjuvant setting.*
>
> *Data from the previously mentioned clinical trials, which have been published, provide solid evidence that:*
>
> - *the occurrence of new primary breast cancers in the contralateral breast was reduced up to 39% ($p<0.00001$),*
> - *the incidence of contralateral breast cancer continued to be reduced with increased duration of tamoxifen treatment, and*
> - *the safety profile for tamoxifen in the reduction of contralateral breast cancer was similar to the recognized adverse event profile for tamoxifen."*

Reviewer Comment: Only two independent clinical trials have demonstrated a statistically significant reduction in the occurrence of contralateral breast cancers in women who were treated with adjuvant tamoxifen. It is an over-interpretation to say that, "The beneficial effects of tamoxifen to reduce the occurrence of new primary breast cancers in the opposite (contralateral) breast have been demonstrated in a substantial number of independent clinical trials." See Reviewers Conclusions.

9. Reviewer's Conclusions

Convincing clinical evidence has been provided in several literature reports of randomized clinical trials (RCTs) that there was a reduction in the occurrence of contralateral breast cancer in early breast cancer patients who were randomized to receive adjuvant tamoxifen for up to 5 years. This evidence is consistent with the claim that, "NOLVADEX is indicated for the reduction of the occurrence of contralateral breast cancer in patients receiving adjuvant NOLVADEX therapy for breast cancer." Current data from clinical trials indicate that the reduction of contralateral breast cancer in women receiving adjuvant tamoxifen was

observed for durations of use up to 5 years. Published data for contralateral breast cancer occurring with more than 5 years of Nolvadex is not available. If this data were available, the numbers of women treated with more than 5 years of tamoxifen in several trials (about 500 women in NSABP B-14 and the Scottish trial) and events would be a relatively small subset of the total data.

10. Recommended Regulatory Action

The supplementary NDA #17-970, S039 for NOLVADEX provides sufficient support for the proposal to revise the tamoxifen package insert to include an additional indication for the reduction of "contralateral breast cancer in women undergoing adjuvant therapy with tamoxifen". Approval for this application is recommended pending review of product labeling by Dr. Julie Beitz (secondary medical reviewer).

/S/

Karen Johnson, M.D., Ph.D. (no longer at FDA)

I have read this review and concur with Dr. Johnson's recommendation for approval of NDA #17-970, S039. A review of product labeling for Nolvadex is contained in a separate document.

/S/

Julie Beitz, M.D. 9/14/98
Date

cc:
NDA #17-970
HFD-150/Division File
HFD-150/J. Beitz
HFD-150/S. Honig
HFD-150/A. Chapman

Attachment I. References


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4. Fisher B, Costantino JP, Redmond CK, et al.: Endometrial Cancer in Tamoxifen-Treated Breast Cancer Patients: Findings From the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994; 86:527-537
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6. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 1992; 339:1-15, 71-85
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8. Mason BH, Holdaway IM, Benton NM, et al.: detection of Contralateral Breast Cancer by Mammography in Women with Previous Breast Cancer and the Impact of Endocrine Therapy. NZ Med J 1993; 106:23-25
9. Leborgne F, Leborgne JH, Ortega B, et al.: Breast Conservation Treatment of Early Stage Breast Cancer: Patterns of Failure. Int J Radiation Oncol Biol Phys 1995; 31:765-775
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Attachment II

Sponsor's Table 3 Incidence of contralateral breast cancer: all patients

| Trial | Tamoxifen patients (n) | CBC in tamoxifen patients (n) | Control patients (n) | CBC in control patients (n) | Median follow-up (months) | Significance |
|---|---|---|---|---|---|---|
| NSABP | 1404 | 56 | 1414 | 82 | 120 | p=0.007 |
| Stockholm | 1372 | 40 | 1357 | 66 | 108 | p=0.008 |
| CRC[a] | 920 | 10 | 934 | 11 | 94 | NA |
| Danish | 661 | 8 | 651 | 10 | 96 | NS |
| Scottish | 661 | 8 | 651 | 14 | 24 to 96 | NA |
| NATO | 551 | 15 | 552 | 17 | 66 | NA |
| Christie (postmenopausal) | 282 | 7 | 306 | 9 | 120 | NA |
| Christie (premenopausal) | 199 | 3 | 174 | 2 | 120 | NA |
| NCCTG (premenopausal) | 198 | 4 | 202 | 1 | 64 | NA |
| NCCTG (postmenopausal) | 71 | 2 | 75 | 3 | 60 | NA |
| South Swedish | 239 | 11 | 236 | 15 | 108 | NS |
| Toronto | 198 | 3 | 202 | 3 | 70 | NA |
| IBSCG IV | 167 | 1 | 153 | 8 | 96 | NA |
| IBSCG III | 153 | 1 | 156 | 1 | 36 | NA |
| GROCTA | 171 | 1 | 165 | 4 | 40 | NA |
| Copenhagen | 164 | 3 | 153 | 4 | 78 | NA |
| ECOG | 85 | 1 | 83 | 5 | 120 | NA |
| Liverpool | 75 | 1 | 83 | 5 | 120 | NA |
| Total | 7774 | 177 | 7741 | 254 | | |
| % total | | 2.3 | | 3.3 | | |

% reduction with tamoxifen = 31

[a]Approximate values based on percentages quoted in the trial

CBC Contralateral breast cancer, NA Not available, NS Not significant