CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 17-970/S018

Trade Name: Nolvadex

Generic Name: Tamoxifen Citrate

Sponsor: ICI Americas Inc.

Approval Date: March 16, 1989

Indications: Effective in the treatment of metastatic breast cancer in women, premenopausal women with metastic breast cancer.

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APPLICATION NUMBER:

NDA 17-970/S018

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APPLICATION NUMBER:
NDA 17-970/S018

APPROVAL LETTER

5111

MAR 16 1989

NDA 17-970/S-018

ICI Americas Inc.
ICI Pharmaceuticals Group
Wilmington, Delaware 19897

Attention: Anthony F. Rogers
Manager, Drug Registration
Drug Regulatory Affairs Department

Dear Mr. Rogers:

Please refer to your April 25, 1988 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nolvadex (tamoxifen citrate) and your February 28, 1989 telephone conversation with Ms. Cathie Schumaker of this Administration.

We acknowledge receipt of your amendments dated July 29, November 1 and 15, December 13, 1988 and February 8, 1989.

We have completed review of this application including the draft labeling submitted on February 8, 1989 and have concluded that adequate information has been presented to demonstrate that Nolvadex is safe and effective for use in premenopausal women with metastatic breast cancer as an alternative to oophorectomy or ovarian irradiation. As agreed, the CLINICAL PHARMACOLOGY section of the package insert will be revised to indicate that the 95% confidence intervals for the analysis of survival data from the Ingle, Pritchard, and Buchanan studies are two-sided.

Accordingly, the application, with the labeling revision described above, is approved effective on the date of this letter.

The revision in the draft package insert represents the terms of the supplemental NDA approval. Marketing the product with this new indication before making the revision, exactly as requested and previously agreed upon, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the FPL when it is available. Please individually mount seven of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FPL for approved NDA 17-970/S-018". Approval of this FPL by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available prior to our receipt of the FPL, revision of that labeling may be required.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Oncology and Radiopharmaceutical Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFD-240
Room 10B-04
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.

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

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig NDA 17-970
HFD-150/Div File
HFD-150/RJustice
HFD-151/CSchumaker/3-01-89 3/9/89
HFD-83
HFD-730
HFD-232(with labeling)
HFD-102/LCarter
R/D Init. by: RLJustice/3-2-89 RJustice 3/9/89
JRJohnson/3-2-89 JRJohnson 3-9-89
RGScully/3-6-89 RGScully 3/9/89
RAJerussi/3-6-89
F/T:mf:3.9.89
Wang #2949E
HFD-100/RTemple
APPROVAL

R.A. Jerussi for
John F. Palmer 3/14/89

R Temple 3/16/89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 17-970/S018

LABELING

63989-02 Rev U 08/89

PROFESSIONAL INFORMATION BROCHURE

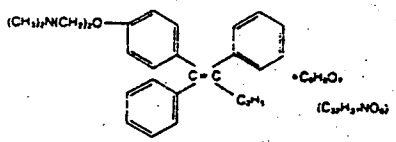
Nolvadex®
10 MG TABLETS

TAMOXIFEN CITRATE

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:



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. 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.

INDICATIONS AND USAGE

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.

NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T_{1-3}, N_{1-3}, M_0). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

CONTRAINDICATIONS

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

WARNINGS

Ocular changes have been reported in a few patients who, as part of a clinical trial, were treated for periods greater than one year with NOLVADEX at doses at least four times the highest recommended daily dose of 40 mg. The ocular changes consist of retinopathy and, in some patients, there are also corneal changes and a decrease in visual acuity.

In addition, a few cases of ocular changes including visual disturbance, cataracts, corneal changes and/or retinopathy have been reported in patients treated with NOLVADEX at recommended doses. It is uncertain if all of these effects are due to NOLVADEX. NOLVADEX has been observed to cause cataracts in rats after 6 months in studies at doses of 20 mg/kg/day (gavage) and higher.

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 single large randomized trial in Sweden of adjuvant tamoxifen 40 mg/day for 2-5 years, an increased incidence of endometrial cancer was noted. Thirteen of 931 tamoxifen treated patients versus 2 of 915 controls developed cancer of the body of the uterus [RR = 6.4 (1.4 - 28), $P < 0.01$]. However, in a review of more than 12,000 patients entered into twelve other large ongoing adjuvant studies (including NSABP B-14) in which patients have received NOLVADEX 20-40 mg/day for periods of 1-5+ years versus control, no increased incidence of cancer of the uterus was seen.

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.

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 made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000-100,000/mm³, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.

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 postmarketing surveillance, T_3 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.

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, presently in progress, has revealed hepatocellular carcinomas at doses of 35 mg/kg/day (206.5 mg/m^2) within 31-37 weeks and cataracts at doses of 20 and 35 mg/kg/day within 6 months.

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 and headache.

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.

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 Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, NOLVADEX or placebo was administered for 2 years to patients 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 arms [illegible]

ECOG Adjuvant Trial
Number of Patients (%)

ADVERSE EFFECT	NOLVADEX (n=91)	Placebo (n=90)
Pain	31 (34%)	34 (38%)
Abnormal Renal Function tests	22 (24%)	19 (21%)
Hot Flashes	17 (19%)	7 (8%)
Leukopenia	14 (15%)	16 (18%)
Nausea and/or Vomiting	13 (14%)	15 (17%)
Edema	10 (11%)	11 (12%)
Thrombocytopenia	9 (10%)	3 (3%)
Fatigue/Tiredness	9 (10%)	8 (9%)
Dyspnea	7 (8%)	6 (7%)
Anorexia	5 (6%)	4 (4%)
Cough	5 (6%)	7 (8%)

In other adjuvant studies, Toronto and NOLVADEX Adjuvant Trial Organization (NATO), patients 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 patients, 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.

	NOLVADEX All Effects Number of Patients (%)	OVARIAN ABLATION All Effects Number of Patients (%)
Adverse Reactions*	n = 104	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 patients had more than one adverse reaction.

OVERDOSAGE

Acute overdosage in humans has not been reported. Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

One or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant NOLVADEX studies noted above, (see Clinical Pharmacology) NOLVADEX was administered for two 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

63989-02 Rev U 08/89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 17-970/S018

SUMMARY BASIS OF APPROVAL

55.1

Orig NDA

Summary Basis of Approval

NDA: 17-970/S-018

Applicant:
ICI Pharmaceuticals Group
Wilmington, Delaware 19897

Drug Generic Name:
tamoxifen citrate

Drug Trade Name:
Nolvadex Tablets

I. Indications for Use:

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.

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). The estrogen and progesterone receptor values may help to predict whether NOLVADEX therapy is likely to be beneficial. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

II. Dosage Form, Route of Administration, and Recommended Dosage:

Nolvadex for oral administration is available as a tablet containing 10 mg of tamoxifen as the citrate. The recommended dosage is one or two 10 mg tablets twice a day (morning and evening). In the three single agent adjuvant studies, Nolvadex was administered for two years. The optimal duration of adjuvant therapy is not known.

III. Manufacturing and Control:

Approved drug. Refer to original Summary Basis of Approval.

IV. Pharmacology:

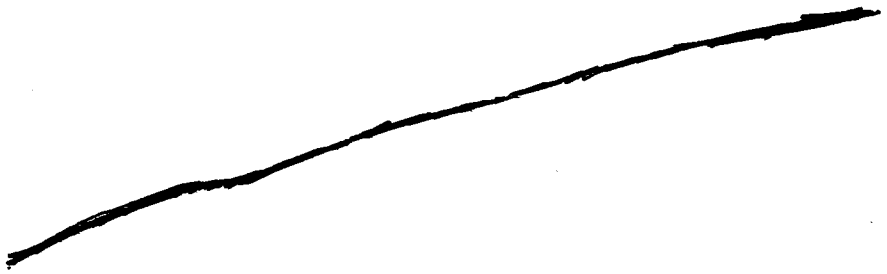
Approved drug. Refer to original Summary Basis of Approval.

V. Medical:

A. General Information

Nolvadex (tamoxifen citrate), a nonsteroidal antiestrogen,

was initially approved on December 30, 1977, for the treatment of metastatic breast cancer in postmenopausal women. On December 10, 1985, tamoxifen was approved for use in combination with cytotoxic chemotherapy for the indication of delaying recurrence of surgically curable breast cancer in postmenopausal women or women age 50 or older with positive axillary nodes. A supplemental application for the indication of delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer (T_{1-3}, N_1, M_0) was approved on December 3, 1986.



b(4)

B. Controlled Clinical Studies

b(4) ——————— the three randomized studies of tamoxifen vs. oophorectomy or ovarian irradiation in premenopausal women with advanced breast cancer.

1. Study NVX 6-341-2 was a prospective, randomized, crossover trial that was conducted as a collaborative effort between the Mayo Clinic and the North Central Cancer Treatment Group. The principal investigator was James N. Engle, M.D. The objective of the study was to compare the therapeutic efficacy of oophorectomy and tamoxifen in premenopausal women with advanced breast cancer.

   Eligibility was limited to premenopausal women with histologically confirmed carcinoma of the breast which was locally inoperable, recurrent, or metastatic and suitable for palliative hormonal therapy. Premenopausal was defined as active menstruation or menstruation within the previous year. Patients may not have received previous hormonal therapy for breast cancer and were required to have measurable or evaluable disease, estrogen receptor positive or unknown tumors, and a performance status of 3 (ECOG) or better.

After stratification by estrogen receptor status, dominant disease, disease-free interval, performance score, prior chemotherapy, indicator disease, and group member, patients were randomized to bilateral oophorectomy or to tamoxifen 10 mg orally b.i.d. Tamoxifen was continued until disease progression. The study accrued patients between May 1978 and April 1984, and the median duration of follow-up was 545 days.

Fifty-four patients were entered on the study before it was closed because of poor accrual. Twenty-seven were randomized to tamoxifen and 27 to oophorectomy. One patient randomized to tamoxifen was ineligible because of a negative estrogen receptor assay. There were no significant differences between the treatment groups in the distribution of stratification factors. The objective response rates were 26% (7/27) for tamoxifen and 37% (10/27) for oophorectomy (p=0.56). The 95% confidence interval (two-sided) for the estimated difference in response rates (tamoxifen - oophorectomy) was -36% to 14%. The median time to best objective response was 116 days for tamoxifen and 126 days for oophorectomy. The median duration of response was 453 days in the tamoxifen group and 476 days in the oophorectomy group.

After disease progression on the primary therapy, 59% (16/27) of the tamoxifen patients and 67% (18/27) of the oophorectomy patients crossed over to the alternate therapy. The response rates for crossover therapy were 31% (5/16) for the tamoxifen patients crossing over to oophorectomy and 11% (2/18) for the oophorectomy patients crossing over to tamoxifen.

Ninety-three percent (25/27) of the tamoxifen patients and 89% (24/27) of the oophorectomy patients had experienced disease progression. The median time to progression during initial therapy was 119 days for tamoxifen patients and 144 days for oophorectomy patients (p=0.63). In a Cox proportional hazards model, the only variable significantly related to time to progression was prior chemotherapy. After adjustment for this covariate, there were no significant differences between treatments in the time to progression (p=0.52). The estimated progression hazard ratio (tamoxifen/oophorectomy) was 1.21 with a two-sided 95% confidence interval of 0.68 to 2.12.

Ninety-three percent (25/27) of patients in both treatment groups had experienced treatment failure. The cause of treatment failure was progressive disease for 96% (24/25) of patients in both groups. The median time to treatment failure was 119 days for tamoxifen patients and 126 days for oophorectomy patients (p=0.73). A Cox proportional hazards analysis again showed that prior chemotherapy was significantly associated with time to treatment failure. After adjustment for prior chemotherapy, treatment was still not significantly related to time to treatment failure (p=0.61). The estimated hazard ratio (tamoxifen/oophorectomy) was 1.16, with a two-sided 95% confidence interval of 0.66 to 2.03.

Fifty-nine percent (16/27) of patients randomized to tamoxifen and 70% (19/27) of patients randomized to oophorectomy had died. The median survival was 809 days for tamoxifen patients and 722 days for oophorectomy patients (p=0.32, log-rank). In a Cox covariate analysis, prior chemotherapy and disease-free interval were significantly associated with survival. After adjustment for these variables, there were still no significant differences in survival (p=0.30). The estimated death hazard ratio (tamoxifen/oophorectomy) was 0.70 with a two-sided 95% confidence interval of 0.35 to 1.38.

With the exception of altered menses, the adverse signs and symptoms were similar in both treatment groups. The most frequently reported adverse effects during primary therapy were hot flashes (tamoxifen 37%, oophorectomy 33%), altered menses (44%, 19%), anorexia (4%, 0%), decreased sense of well-being (4%, 0%), edema (0%, 4%), headache (4%, 0%), nausea (4%, 0%), and vaginal bleeding (4%, 0%). The low incidence of altered menses in the oophorectomy group was apparently due to under-reporting of an expected consequence of oophorectomy.

Although this study was terminated prior to achieving its planned patient accrual, it did provide evidence that the objective response rate, time to progression, time to treatment failure, and survival with tamoxifen were not likely to be much worse than with oophorectomy. Treatment with tamoxifen appeared to be well-tolerated.

2. Study NVX 0-393-1 was a prospective, randomized, crossover trial sponsored by the National Cancer Institute of Canada and conducted in eight participating institutions. The principal investigator was Kathleen Pritchard, M.D. The primary objective was to compare the response rate, time to progression, and survival of premenopausal women with metastatic breast cancer treated with tamoxifen or ovarian ablation.

Eligibility was limited to premenopausal women with histologically documented, locally advanced or metastatic breast cancer who were candidates for ovarian ablation (positive or unknown estrogen and/or progesterone receptors). Premenopausal was defined as regular menstrual periods within 6 months of starting therapy or age less than 50 in patients who had a hysterectomy but not an oophorectomy. Although patients may not have received hormonal treatment for their advanced disease, they may have received tamoxifen or prednisone as part of an adjuvant treatment program if the drug had been discontinued at least one year prior to study entry. Patients who had previously received chemotherapy must have been off treatment for at least 4 weeks. Patients were also required to have a performance status greater than 20 (Karnofsky), measurable or evaluable disease, and an expected survival of more than 2 months.

After stratification by receptor status, metastatic site, and prior hormonal therapy, patients were randomized to tamoxifen or ovarian ablation. Tamoxifen was administered orally at a dose of 20 mg b.i.d. until disease progression. Ovarian ablation was to be performed surgically or by ovarian irradiation (1500 rad in 5 consecutive days). The study accrued patients between 9/8/81 and 4/25/84, and the overall median follow-up was 623 days.

Thirty-nine patients were entered on the study before it was closed because of poor patient accrual. Twenty were randomized to tamoxifen and 19 were randomized to ovarian ablation. Although two patients randomized to tamoxifen did not meet the eligibility criteria, they were included in the analysis. One had not been off adjuvant tamoxifen therapy for one year prior to study entry and the other did not have a regular menstrual period within

6 months of starting the study. Two additional patients refused the randomized therapy. One was randomized to tamoxifen but had an ovarian ablation, and the other was randomized to ovarian ablation but received tamoxifen instead. In the statistical analyses, both patients were included in the group to which they were randomized. There were no significant differences between treatment groups in receptor status, dominant disease site, prior therapy, center, age, weight, disease-free interval from mastectomy, baseline performance score, or disease type. b(4)

Five patients (4 tamoxifen and 1 ovarian ablation) were not evaluable for response but were included in the denominator. The objective response rates were 15% (3/20) for tamoxifen and 11% (2/19) for ovarian ablation (p=1.0). The 95% confidence interval (two-sided) for the estimated difference in response rates (tamoxifen - ovarian ablation) was -17% to 25%. The times to response were 619, 503, and 182 days for the tamoxifen responders and 433 and 95 days for the ovarian ablation responders. The median duration of response was 1080 days in the tamoxifen group and 698 days in the ovarian ablation group.

Following disease progression on the primary therapy, 55% (11/20) of the tamoxifen patients and 95% (18/19) of the ovarian ablation patients received the crossover treatment. The only response occurred in a patient with stable disease after ovarian ablation who had a partial response after crossover therapy with tamoxifen.

Ninety percent (18/20) of patients initially treated with tamoxifen and all of the 19 patients initially receiving ovarian ablation had experienced treatment failure. Progressive disease was the cause in 78% (14/18) of the tamoxifen patients and in 95% (18/19) of the ovarian ablation patients. The median time to treatment failure was 196 days for tamoxifen and 128 days for ovarian ablation (p=0.60). In a Cox proportional hazards model with treatment and receptor status as covariates, the estimated treatment failure hazard ratio (tamoxifen/ovarian ablation) was 0.87, with a two-sided 95% confidence interval of 0.44 to 1.72.

Sixty percent (12/20) of the tamoxifen patients and 47% (9/19) of the ovarian ablation patients had died. The median survival was 806 days for the tamoxifen patients and 864 days for the ovarian ablation patients (p=0.62, log-rank). In a Cox covariate analysis, the estimated death hazard ratio (tamoxifen/ovarian ablation) was 1.48, with a two-sided 95% confidence interval of 0.61 to 3.56.

The most frequently reported adverse effects during primary therapy were amenorrhea (tamoxifen 37%, ovarian ablation 78%), flushes (32%, 44%), bone pain (32%, 33%), and menstrual disorders (32%, 22%). Two patients randomized to ovarian ablation had an oophorectomy and 3 patients randomized to tamoxifen had an oophorectomy at crossover. All 5 patients were found to have ovarian cysts which were asymptomatic and not detectable on pelvic examination. Therefore, there was no evidence of an association between ovarian cysts and tamoxifen therapy. One patient who was randomized to tamoxifen developed a second primary (infiltrating ductal carcinoma) in the contralateral breast.

Although this study was terminated prior to completion because of poor patient accrual, it also provided evidence that the objective response rate, time to treatment failure, and survival with tamoxifen were not likely to be much worse than with ovarian ablation.

3. Study UK 4674/0032 was a prospective, randomized, crossover trial that was conducted in eight participating institutions in the United Kingdom. The principal investigator was Dr. R. B. Buchanan, Wessex Radiotherapy Centre, Royal South Hants Hospital, Southampton. The objective of the study was to compare tumor response and time to relapse with oophorectomy or Nolvadex in premenopausal patients with advanced breast cancer.

Eligibility was limited to premenopausal women with histologically proven advanced breast cancer and measurable disease. Premenopausal was defined as regular menstruation, or a menstrual period within the previous 12 months and one of 2 Follicle Stimulating Hormone (FSH) levels within the premenopausal range, or age less than 50 and prior hysterectomy or cytotoxic adjuvant therapy. Adjuvant chemotherapy or hormonal therapy must have

been discontinued at least 6 weeks before study entry. Patients may not have had an oophorectomy or previous treatment for their advanced disease.

Patients were randomized by center to surgical oophorectomy or tamoxifen 20 mg orally b.i.d. If possible, tamoxifen was to be administered for at least 3 months. Patients improving or responding at 3 months were to continue tamoxifen. Patients with stable disease or progression at 3 months were to be taken off study. The study accrued patients between September 1979 and June 1983.

One hundred and twenty-two patients were entered on the study. Sixty-one were randomized to tamoxifen and 61 to oophorectomy. Three patients in each group were found to be ineligible. Five patients in the tamoxifen group and 7 patients in the oophorectomy group were not evaluable for response. There were no significant differences between treatment groups for disease-free interval from mastectomy, prior adjuvant therapy, baseline performance score, general health questionnaire score, estrogen receptor status, disease site, or age.

The objective response rates were 21% (13/61) with tamoxifen and 18% (11/61) with oophorectomy ($p=0.82$). The median duration of response was 456 days for tamoxifen and 212 days for oophorectomy. The 95% confidence interval (two-sided) for the estimated difference in response rates (tamoxifen - oophorectomy) was -11% to 17%.

Following disease progression with primary therapy, 11% (7/61) of the tamoxifen patients and 20% (12/61) of the oophorectomy patients received the crossover therapy. One patient randomized to tamoxifen had a complete response lasting 4 months after crossover to oophorectomy. One patient randomized to oophorectomy had a partial response lasting 6 months after crossover to tamoxifen.

Eighty of the 122 patients had experienced disease progression. The estimated hazard ratio for time to progression (tamoxifen/oophorectomy) was 0.92, with a two-sided 95% confidence interval of 0.59 to 1.43. There were no significant differences between the treatment groups in time to treatment failure ($p=0.71$). The estimated treatment failure hazard ratio (tamoxifen/oophorectomy) was 0.93, with a two-sided 95% confidence interval of 0.62 to 1.38.

Eighty-four percent (51/61) of patients randomized to tamoxifen and 85% (52/61) of patients randomized to oophorectomy had died. The median survival was 450 days for tamoxifen and 626 days for oophorectomy (p=0.78, log-rank). The estimated death hazard ratio (tamoxifen/oophorectomy) was 1.06 with a two-sided 95% confidence interval of 0.72 to 1.56

Tamoxifen was again well-tolerated. Although no patients withdrew from the study because of an adverse event, 3 patients had their tamoxifen dose reduced to 20 mg daily. The most frequent adverse reactions were altered menses (tamoxifen 36%, oophorectomy 100%), hot flushes (21%, 38%), fatigue (5%, 0%), skeletal/muscular pain (5%, 0%), edema (3%, 0%), nausea (3%, 2%), and loss of libido (0%, 4%).

This study provided additional evidence that the response rate, time to progression, time to treatment failure, and survival with tamoxifen was not likely to be much worse than with oophorectomy.

4. Overview Analysis of Controlled Studies

The Ingle, Pritchard, and Buchanan studies were the only randomized trials of tamoxifen vs. oophorectomy or ovarian irradiation in premenopausal women with advanced breast cancer. Because of the small number of patients, especially in the Ingle and Pritchard studies, an overview analysis was used to provide a more precise estimate of treatment effects.

A total of 215 patients were entered on the studies. One hundred and eight were randomized to tamoxifen and 107 were randomized to ovarian ablation. A weighted average of the differences in response rates for the individual studies was used in the overview analysis of best objective tumor response rates. The estimated adjusted difference (tamoxifen - ovarian ablation) in responses rates was 1% with a 95% confidence interval (two-sided) of -10% to 12%. The hazard ratio for time to progression (tamoxifen/ovarian ablation) was 0.92 with a two-sided 95% confidence interval of 0.68 to 1.26. The hazard ratio for the time to treatment failure was 0.97 with a two-sided 95% confidence interval of 0.70 to 1.26. The estimated death hazard ratio was 1.00 with a two-sided 95% confidence interval of 0.73 to 1.37.

C. Uncontrolled Clinical Studies

1. Study NVX 7-236-3-1 was a non-randomized, phase II, crossover trial that was conducted in four hospitals affiliated with the University of Toronto. The principal investigator was J. W. Meakin, M.D., of the Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Canada. The objectives were to assess the effectiveness of tamoxifen in the management of premenopausal women with metastatic breast cancer and to determine whether patients who initially failed to respond to tamoxifen would respond to ovarian ablation.

Eligibility was limited to premenopausal women with histologically documented breast cancer and metastatic disease who were candidates for ovarian ablation. Premenopausal was defined as regular menstrual periods within 6 months of starting therapy or age less than 50 and a previous hysterectomy without an oophorectomy. Although patients may not have received hormonal therapy, they may have received chemotherapy if they were off treatment for at least four weeks. Patients were also required to have a performance status greater than 10 (Karofsky scale), measurable or evaluable disease, and an expected survival of greater than two months. Patients with estrogen receptor negative tumors were eligible for the study at the discretion of their attending physician.

All patients were assigned to intial treatment with tamoxifen 20 mg b.i.d. orally for a minimum of 8 weeks. If rapid progression occurred during this period, tamoxifen was to be stopped and patients were to undergo ovarian ablation as soon as possible. The study accrued patients between August 1977 and April 1981. The median follow-up was 538 days.

Sixty-five patients were entered on the study and 12 were ineligible. The median duration of tamoxifen therapy was 91 days. There were 4 complete and 7 partial responses for an overall response rate of 17% (11/65). The 95% confidence interval for response rate was 8% to 26%.

Following disease progression with tamoxifen, 39 patients had ovarian ablation, either by surgical oophorectomy (22) or by radiation ablation (17).

Five of the 21 evaluable patients who did not respond to tamoxifen responded to ovarian ablation. Five of 9 patients that responded to tamoxifen had a partial response after ovarian ablation.

Ninety-eight percent (64/65) of the patients had experienced treatment failure. The cause of treatment failure was progressive disease (73%), progressive disease plus toxicity (3%), withdrawal due to toxicity (5%), patient refusal (3%), deteriorating condition (13%), and absence of metastatic disease (3%). The median time to treatment failure was 50 days.

Eighty percent (52/65) of the patients had died. Death was attributed to breast cancer in 33% (17) and to hemorrhage, myocardial infarction, and renal failure in one patient. The cause of death was unknown in 65% (34) patients. The median survival was 674 days.

Five patients (8%) discontinued therapy because of adverse effects. The most frequently reported adverse reactions were flushes (29%), menstrual disorders (23%), amenorrhea (20%), nausea or vomiting (20%), treatment-induced disease flare (8%), depression (5%), hirsutism (5%), edema (5%), constipation (3%), hypercalcemia (3%), and sweating (3%). Twenty-two patients had an oophorectomy following tamoxifen failure and 8 (36%) were noted to have ovarian cysts. The cysts were asymptomatic and not detectable on pelvic examination. Because there was no control group, the relationship to tamoxifen therapy could not be determined.

The objective response rates and adverse effects with tamoxifen in this study were similar to those reported for the 3 randomized studies. The study provided supportive evidence of tamoxifen's safety and efficacy in the palliation of metastatic breast cancer in premenopausal women.

2. Literature Review of Tamoxifen Therapy in Premenopausal Women with Advanced Breast Cancer

The applicant reviewed all of the studies in which premenopausal patients received tamoxifen as treatment of advanced breast cancer. A study was included in the review if the number of patients

evaluated for response was included and if the response criteria and response results were provided. Besides the Meakin study, there were 28 studies which met these criteria. The overall objective response rate was 32% (104/323).

3. Literature Review of Oophorectomy/Ovarian Ablation in Premenopausal Women with Advanced Breast Cancer

The applicant also reviewed the literature on oophorectomy or ovarian irradiation in the treatment of premenopausal women with advanced breast cancer. The overall objective response rate in 10 major trials was 36% (565/1566).

4. Literature Review of the Hormonal Effects of Tamoxifen in Premenopausal Patients

The applicant reviewed the literature on the hormonal effects of tamoxifen in premenopausal women. The studies were conducted in volunteers, anovulatory or infertile women, patients with benign breast disease, patients receiving adjuvant chemotherapy with tamoxifen, and patients with advanced breast cancer. Although an occasional study reported increases in (FSH), Luteinizing Hormone (LH), or progesterone, most studies found no significant changes in serum or plasma FSH, LH, prolactin, or progesterone levels. In contrast, there were 11 reports of significant increases in serum or plasma estrogens with tamoxifen therapy at doses of 20 mg/day or greater. However, the data from the randomized studies did not support the theoretical possibility that hyperestrogenemia could stimulate tumor growth and have an adverse effect on time to progression or survival.

VI. Oncologic Drugs Advisory Committee Meeting:

The supplemental application was presented to the Oncologic Drugs Advisory Committee on December 20, 1988. The Committee voted unanimously to recommend approval of the new indication.

VII. Approved Package Insert:

A copy is attached.

Wang #0097R