PROFESSIONAL INFORMATION BROCHURE

T-10 10/28/98 **SIC XXXXX-XX**

Nolvadex®
TAMOXIFEN CITRATE

DESCRIPTION

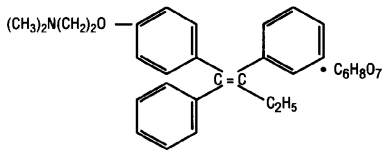
NOLVADEX_ (tamoxifen citrate) Tablets, a nonsteroidal antiestrogen, are for oral administration. NOLVADEX Tablets are available as:

10 mg Tablets. Each tablet contains 15.2 mg of tamoxifen citrate which is equivalent to 10 mg of tamoxifen.

20 mg Tablets. Each tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen.

Inactive Ingredients: carboxymethylcellulose calcium, magnesium stearate, mannitol and starch.

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:



($C_{32}H_{37}NO_8$)

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.

CLINICAL PHARMACOLOGY

NOLVADEX is a nonsteroidal agent that 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 anti-tumor effects by binding the estrogen receptors.

In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

Tamoxifen is extensively metabolized after oral administration. Studies in women receiving 20 mg of ^{14}C tamoxifen have shown that approximately 65% of the administered dose is excreted from the body over a period of 2 weeks with fecal excretion the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma.

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for three months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for three months are 122 ng/mL (range 71-183 ng/mL) and 353 ng/mL (range 152-706 ng/mL), respectively. After initiation of therapy, steady state concentrations for tamoxifen are achieved in about 4 weeks and steady state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite.

In a 3-month crossover steady-state bioavailability study with NOLVADEX 10 mg twice a day versus NOLVADEX 20 mg given once daily, NOLVADEX 20 mg taken once daily had similar bioavailability to NOLVADEX 10 mg taken twice a day.

• Clinical Studies - Metastatic Breast Cancer:

Premenopausal Women (NOLVADEX vs. Ablation) - Three prospective, randomized studies (Ingle, Pritchard, 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, but the data from the randomized studies do not suggest an adverse effect of this increase. A limited number of premenopausal patients with disease progression during NOLVADEX therapy responded to subsequent ovarian ablation.

Male Breast Cancer - Published results from 122 patients (119 evaluable) and case reports in 16 patients (13 evaluable) treated with NOLVADEX have shown that NOLVADEX is effective for the palliative treatment of male breast cancer. Sixty-six of these 132 evaluable patients responded to NOLVADEX which constitutes a 50% objective response rate.

• Clinical Studies - Adjuvant Breast Cancer

Overview - The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted worldwide overviews of systemic adjuvant therapy for early breast cancer in 1985, 1990, and again in 1995. In 1998, 10-year outcome data were reported for 36,689 women in 55 randomized trials of adjuvant NOLVADEX using doses of 20-40 mg/day for 1-5+ years. Twenty-five percent of patients received one year or less of trial treatment, 52% received 2 years, and 23% received about 5 years. Forty-eight percent of tumors were estrogen receptor (ER) positive (> 10 fmol/mg), 21% were ER poor (< 10 fmol/l), and 31% were ER unknown. Among 29,441 patients with ER positive or unknown breast cancer, 58% were entered into trials comparing NOLVADEX to no adjuvant therapy and 42% were entered into trials comparing NOLVADEX in combination with chemotherapy vs. the same chemotherapy alone. Among these patients, 54% had node positive disease and 46% had node negative disease.

Among women with ER positive or unknown breast cancer and positive nodes who received about 5 years of treatment, overall survival at 10 years was 61.4% for NOLVADEX vs. 50.5% for control (logrank $2p < 0.00001$). At ten years, the recurrence rate was 59.7% for NOLVADEX vs. 44.5% for control (logrank $2p < 0.00001$). Among women with ER positive or unknown breast cancer and negative nodes who received about 5 years of treatment, overall survival at 10 years was 78.9% for NOLVADEX vs. 73.3% for control (logrank $2p < 0.00001$). At ten years, the recurrence rate was 79.2% for NOLVADEX vs. 64.3% for control (logrank $2p < 0.00001$).

The effect of the scheduled duration of tamoxifen may be described as follows. In women with ER positive or unknown breast cancer receiving 1 year or less, 2 years or about 5 years of NOLVADEX, the proportional reductions in mortality were 12%, 17% and 26%, respectively (trend significant at $2p < 0.003$). The corresponding reductions in breast cancer recurrence were 21%, 29% and 47% (trend significant at $2p < 0.00001$).

Benefit is less clear for women with ER poor breast cancer in whom the proportional reduction in recurrence was 10% ($2p=0.007$) for all durations taken together, or 9% ($2p=0.02$) if contralateral breast cancers are excluded. The corresponding reduction in mortality was 6% (NS). The effects of about 5 years of NOLVADEX on recurrence and mortality were similar regardless of age and concurrent chemotherapy. There was no indication that doses greater than 20 mg per day were more effective.

Node Positive - Individual Studies - 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).

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. The NATO study also demonstrated an overall survival benefit.

Node Negative - Individual Studies - NSABP B-14, a prospective, double-blind, randomized study, compared NOLVADEX to placebo in women with axillary node-negative, estrogen-receptor positive (≥10 fmol/mg cytosol protein) breast cancer (as adjuvant therapy, following total mastectomy and axillary dissection, or segmental resection, axillary dissection, and breast radiation). After five years of treatment, there was a significant improvement in disease-free survival in women receiving NOLVADEX. This benefit was apparent both in women under age 50 and in women at or beyond age 50.

One additional randomized study (NATO) demonstrated improved disease-free survival for NOLVADEX compared to no adjuvant therapy following total mastectomy and axillary dissection in postmenopausal women with axillary node-negative breast cancer. In this study, the benefits of NOLVADEX appeared to be independent of estrogen receptor status.

Duration of Therapy - In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy.

In the NSABP B-14 trial, in which patients were randomized to NOLVADEX 20 mg/day for 5 years versus placebo and were disease-free at the end of this 5-year period were offered rerandomization to an additional five years of NOLVADEX or placebo. With four years of follow-up after this rerandomization, 92% of the women that received five years of NOLVADEX wereare alive and disease-free, compared to 86% of the women scheduled to receive 10 years of NOLVADEX (p=0.003). Overall survivals were 96% and 94%, respectively (p=0.08). Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit.

A Scottish trial of five years of tamoxifen versus indefinite treatment found a disease-free survival of 70% in the five-year group and 61% in the indefinite group, with 6.2 years median follow-up (HR=1.27, 95% CI 0.87-1.85).

In a large randomized trial conducted by the Swedish Breast Cancer Cooperative Group of adjuvant NOLVADEX 40 mg/day for 2 or 5 years, overall survival at ten years was estimated to be 80% in the patients in the five-year tamoxifen group, compared with 74% among corresponding patients in the two-year treatment group (p=0.03). Disease-free survival at ten years was 73% in the five-year group and 67%

in the two-year group (p=0.009). Compared with two years of tamoxifen treatment, five years of treatment resulted in a slightly greater reduction in the incidence of contralateral breast cancer at ten years, but this difference was not statistically significant.

Contralateral Breast Cancer - The incidence of contralateral breast cancer is reduced in breast cancer patients (premenopausal and postmenopausal) receiving NOLVADEX compared to placebo. Data on contralateral breast cancer are available from 32,422 out of 36,689 patients in the 1995 overview analysis of the Early Breast Cancer Trialists Collaborative Group (EBCTCG). In clinical trials with NOLVADEX of 1 year or less, 2 years, and about 5 years duration, the proportional reductions in the incidence rate of contralateral breast cancer among women receiving NOLVADEX were 13% (NS), 26% ($2p = 0.004$) and 47% ($2p < 0.00001$), with a significant trend favoring longer tamoxifen duration ($2p = 0.008$). The proportional reduction in the incidence of contralateral breast cancer were independent of age and ER status of the primary tumor. Treatment with about 5 years of NOLVADEX reduced the annual incidence rate of contralateral breast cancer from 7.6 per 1000 patients in the control group compared with 3.9 per 1000 patients in the tamoxifen group.

In a large randomized trial in Sweden (the Stockholm Trial) of adjuvant NOLVADEX 40 mg/day for 2-5 years, the incidence of second primary breast tumors was reduced 40% ($p<0.008$) on tamoxifen compared to control. 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 was also significantly reduced ($p<0.01$). In NSABP B-14, the annual rate of contralateral breast cancer was 8.0 per 1000 patients in the placebo group compared with 5.0 per 1000 patients in the tamoxifen group, at 10 years after first randomization.

Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women: The Breast Cancer Prevention Trial (BCPT, NSABP P-1) was a double-blind, randomized, placebo controlled trial with a primary objective to determine whether five years of NOLVADEX therapy (20 mg/day)would reduce the incidence of invasive breast cancer in women at high risk for the disease. (See INDICATIONS AND USAGE). Secondary objectives included an evaluation of the incidence of ischemic heart disease; the effects on the incidence of bone fractures; and other events that might be associated with the use of NOLVADEX, including: endometrial cancer, pulmonary embolus, deep vein thrombosis**,** stroke, and cataract formation and surgery (See WARNINGS).

The Gail Model was used to calculate predicted breast cancer risk for women who were less than 60 years of age and did not have lobular carcinoma in situ (LCIS). The following risk factors were used: age;

number of first-degree female relatives with breast cancer; previous breast biopsies; presence or absence of atypical hyperplasia; nulliparity; age at first live birth; and age at menarche. A 5-year predicted risk of breast cancer of $\geq$ 1.67% was required for entry into the trial.

In this trial, 13,388 women of at least 35 years of age were randomized to receive either NOLVADEX or placebo for five years. The median duration of treatment was 3.5 years. As of January 31, 1998, follow-up data is available for 13,114 women. Twenty-seven percent of women randomized to placebo (1782) and 24% of women randomized to NOLVADEX (1596) completed 5 years of therapy. The demographic characteristics of women on the trial with follow-up data are shown in Table 1.

Table 1. Demographic Characteristics of Women in the NSABP P-1 Trial

Characteristic	Placebo		Tamoxifen	
	#	%	#	%
Age (yrs.)				
35-39	184	3	158	2
40-49	2,394	36	2,411	37
50-59	2,011	31	2,019	31
60-69	1,588	24	1,563	24
≥70	393	6	393	6
Age at first live birth(yrs.)				
Nulliparous	1,202	18	1,205	18
12-19	915	14	946	15
20-24	2,448	37	2,449	37
25-29	1,399	21	1,367	21
≥30	606	9	577	9
Race				
White	6,333	96	6,323	96
Black	109	2	103	2
Other	128	2	118	2
Age at menarche				
≥14	1,243	19	1,170	18
12-13	3,610	55	3,610	55
≤11	1,717	26	1,764	27
# of first degree relatives with breast cancer				
0	1,584	24	1,525	23
1	3,714	57	3,744	57
2+	1,272	19	1,275	20
Prior Hysterectomy				
No	4173	63.5	4018	62.4
Yes	2397	36.5	2464	37.7
# of previous breast biopsies				
0	2,935	45	2,923	45
1	1,833	28	1,850	28
≥ 2	1,802	27	1,771	27
History of atypical hyperplasia in the breast				
No	5,958	91	5,969	91
Yes	612	9	575	9
History of LCIS at entry				
No	6,165	94	6,135	94
Yes	405	6	409	6
5-year predicted breast cancer risk (%)				
≤2.00	1,646	25	1,626	25
2.01-3.00	2,028	31	2,057	31
3.01-5.00	1,787	27	1,707	26
≥5.01	1,109	17	1,162	18
Total	6,570	100.0	6,544	100.0

Results are shown in Table 2. After a median follow-up of 4.2 years, the incidence of invasive breast cancer was reduced by 44% among women assigned to NOLVADEX (86 cases-NOLVADEX, 156 cases-placebo; $p<0.00001$; relative risk (RR)=0.56, 95% CI: 0.43-0.72). A reduction in the incidence of breast cancer was seen in each prospectively specified age group ($\leq$ 49, 50-59, $\geq$ 60), in women with or without LCIS, and in each of the absolute risk levels specified in Table 2. A non-significant decrease in the incidence of ductal carcinoma in situ (DCIS) was seen (23-NOLVADEX, 35-placebo; RR=0.66; 95% CI: 0.39-1.11).

There was no statistically significant difference in the number of myocardial infarctions, severe angina, or acute ischemic cardiac events between the two groups (61-NOLVADEX, 59-placebo; RR=1.04, 95% CI 0.73-1.49).

No overall difference in mortality (53 deaths in NOLVADEX group versus 65 deaths in placebo group) was present. No difference in breast cancer-related mortality was observed (4 deaths in NOLVADEX group versus 5 deaths in placebo group).

Although there was a non-significant reduction in the number of hip fractures (9 on NOLVADEX, 20 on placebo) in the NOLVADEX group, the number of wrist fractures was similar in the two treatment groups (69 on NOLVADEX, 74 on placebo). No information regarding bone mineral density or other markers of osteoporosis is available.

The risks of NOLVADEX therapy include endometrial cancer, DVT, PE, stroke, cataract formation and cataract surgery (See Table 2). In the NSABP P-1 trial, 33 cases of endometrial cancer were observed in the NOLVADEX group versus 14 in the placebo group (RR=2.48, 95% CI 1.27-4.92). Deep vein thrombosis was observed in 30 women receiving NOLVADEX versus 19 in women receiving placebo (RR=1.59, 95% CI 0.86-2.98). Eighteen cases of pulmonary embolism were observed in the NOLVADEX group versus 6 in the placebo group (RR=3.01, 95% CI 1.15-9.27). There were 34 strokes on the NOLVADEX arm and 24 on the placebo arm (RR 1.42; 95% CI 0.82-2.51). Cataract formation in women without cataracts at baseline was observed in 540 women taking NOLVADEX versus 483 women receiving placebo (RR=1.13, 95% CI 1.00-1.28). Cataract surgery (with or without cataracts at baseline) was performed in 201 women taking NOLVADEX versus 129 women receiving placebo (RR=1.51, 95% CI 1.21-1.89) (See WARNINGS).

Table 2 summarizes the major outcomes of the NSABP P-1 trial. For each endpoint, the following results are presented: the number of events and rate per 1000 women per year for the placebo and NOLVADEX groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between NOLVADEX and placebo. Relative risks less than 1.0 indicate a benefit of NOLVADEX therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits or risks of NOLVADEX therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists. For most participants, multiple risk factors would have been required for eligibility. This table considers risk factors individually, regardless of other co-existing risk factors, for women who developed breast cancer. The five-year predicted absolute breast cancer risk accounts for multiple risk factors in an individual and should provide the best estimate of individual benefit (See INDICATIONS AND USAGE)

Table 2: Major Outcomes of the NSABP P-1 Trial

	# OF EVENTS		RATE/1000 WOMEN/YEAR			95% CI
TYPE OF EVENT	PLACEBO	NOLVADEX	PLACEBO	NOLVADEX	RR	LIMITS
Invasive Breast Cancer	156	86	6.49	3.58	0.56	0.43-0.72
Age ≤49	59	38	6.34	4.11	0.65	0.43-0.98
Age 50-59	46	25	6.31	3.53	0.56	0.35-0.91
Age ≥60	51	23	7.17	3.22	0.45	0.27-0.74
Risk Factors for Breast Cancer						
History, LCIS						
No	140	78	6.23	3.51	0.56	0.43-0.74
Yes	16	8	12.73	6.33	0.50	0.21-1.17
History, Atypical Hyperplasia						
No	138	84	6.37	3.89	0.61	0.47-0.80
Yes	18	2	8.69	1.05	0.12	0.03-0.52
No. First Degree Relatives						
0	32	17	5.97	3.26	0.55	0.30-0.98
1	80	45	5.81	3.31	0.57	0.40-0.82
2	35	18	8.92	4.67	0.52	0.30-0.92
≥3	9	6	13.33	7.58	0.57	0.20-1.59
5-Year Predicted Breast Cancer Risk (as calculated by the Gail Model)						
≤2.00%	31	13	5.36	2.26	0.42	0.22-0.81
2.01-3.00%	39	28	5.25	3.83	0.73	0.45-1.18
3.01-5.00%	36	26	5.37	4.06	0.76	0.46-1.26
≥5.00%	50	19	13.15	4.71	0.36	0.21-0.61
DCIS	35	23	1.47	0.97	0.66	0.39-1.11
Fractures (protocol-specified sites)	92[1]	76[1]	3.87	3.20	0.61	0.83-1.12
Hip	20	9[2]	0.84	0.38	0.45	0.18-1.04
Wrist[2]	74	69	3.11	2.91	0.93	0.67-1.29
Total Ischemic Events	59	61	2.47	2.57	1.04	0.71-1.51
Myocardial Infarction	27	27	1.13	1.13	1.00	0.57-1.78
Fatal	8	7	0.33	0.29	0.88	0.27-2.77
Nonfatal	19	20	0.79	0.84	1.06	0.54-2.09
Angina[33]	12	12	0.50	0.50	1.00	0.41-2.44
Acute Ischemic Syndrome[44]	20	22	0.84	0.92	1.11	0.58-2.13
Invasive Endometrial Cancer (among women without a hysterectomy)	14	33	0.92	2.29	2.48	1.27-4.92
Stroke[55]	24	34	1.00	1.43	1.42	0.82-2.51
Transient Ischemic Attack	21	18	0.88	0.75	0.86	0.43-1.70
Pulmonary Emboli[6]	6	18	0.25	0.75	3.01	1.15-9.27
Deep-Vein Thrombosis[7]	19	30	0.79	1.26	1.59	0.86-2.98
Cataracts Developing on Study[8]	483	540	22.51	25.41	1.13	1.00-1.28
Underwent Cataract Surgery[8]	63	101	31.43	46.62	1.48	1.08-2.03
Underwent Cataract Surgery[9]	129	201	37.58	56.81	1.51	1.21-1.89

[1]Two women had hip and wrist fractures
[2] Includes Colles' and other lower radius fractures
[3]Requiring angioplasty or CABG
[4]New Q-wave on ECG; no angina or elevation of serum enzymes; or angina requiring hospitalization without surgery
[5]Seven cases were fatal; three in the placebo group and four in the NOLVADEX group
[6]Three cases in the NOLVADEX group were fatal
[7]All but three cases in each group required hospitalization
[8]Based on women without cataracts at baseline (6230 Placebo, 6199 NOLVADEX)
[9]All women. (6707-Placebo, 6681-NOLVADEX)

Table 3 describes the characteristics of the breast cancers in the NSABP P-1 trial and includes tumor size, nodal status, ER status. NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors.

Table 3: Characteristics of Breast Cancer in NSABP P-1 Trial

Staging Parameter	Placebo N=156154	Tamoxifen N=8685	Total N=242239
Tumor size:			
T1	117	60	177
T2	28	20	48
T3	7	3	10
T4	1	2	3
Unknown	3	10	4
Nodal status:			
Negative	103	56	159
1-3 positive nodes	29	14	43
≥ 4 positive nodes	10	12	22
Unknown	14	4	18
Stage:			
I	88	47	135
II: node negative	15	9	24
II: node positive	33	22	55
III	6	4	10
IV	2[1]	1	3
Unknown	12	3	15
Estrogen receptor:			
Positive	115	38	153
Negative	27	36	63
Unknown	14	12	26

[1] 1 participant presented with a suspicious bone scan but did not have documented metastases. She subsequently died of metastatic breast cancer..

Interim results from two trials in addition to the NSABP P-1 trial examining the effects of tamoxifen in reducing breast cancer incidence have been reported.

The first was the Italian Tamoxifen Prevention trial. In this trial women between the ages of 35 and 70, who had had a total hysterectomy, were randomized to receive 20 mg tamoxifen or matching placebo for 5 years. The primary endpoints were occurrence of, and death from, invasive breast cancer. Women without any specific risk factors for breast cancer were to be entered. Between 1992 and 1997, 5408 women were randomized. Hormone Replacement Therapy (HRT) was used in 14% of participants. The trial closed in 1997 due to the large number of dropouts during the first year of treatment (26%). After 46 months of follow-up there were 22 breast cancers in women on placebo and 19 in women on tamoxifen. Although no decrease in breast cancer incidence was observed, there was a trend for a reduction in breast cancer among women receiving protocol therapy for at least one year (19-placebo, 11- tamoxifen). The small numbers of participants along with the low level of risk in this otherwise healthy group precluded an adequate assessment of the effect of tamoxifen in reducing the incidence of breast cancer.

The second trial, the Royal Marsden Trial (RMT) was reported as an interim analysis. The RMT was, begun in 1986 as a feasibility study of whether larger scale trials could be mounted. The trial was subsequently extended to a pilot trial to accrue additional participants to further assess the safety of tamoxifen. 2471 women were entered between 1986 and 1996; they were selected on the basis of a family history of breast cancer. HRT was used in 40% of participants. In this trial, with a 70-month median follow-up, 34 and 36 breast cancers (8 noninvasive, 4 on each arm) were observed among women on tamoxifen and placebo, respectively. Patients in this trial were younger than those in the NSABP P-1 trial and may have been more likely to develop ER(-) tumors, which are unlikely to be reduced in number by tamoxifen therapy. Although women were selected on the basis of family history and were thought to have a high risk of breast cancer, few events occurred, reducing the statistical power of the study. These factors are potential reasons why the RMT may not have provided an adequate assessment of the effectiveness of tamoxifen in reducing the incidence of breast cancer.

In these trials, an increased number of cases of deep vein thrombosis, pulmonary embolus, stroke, and endometrial cancer were observed on the tamoxifen arm compared to the placebo arm. The frequency of events was consistent with the safety data observed in the NSABP P-1 trial.

INDICATIONS AND USAGE

Metastatic Breast Cancer: NOLVADEX is effective in the treatment of metastatic breast cancer in women and men. 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.

Adjuvant Treatment of Breast Cancer: NOLVADEX is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

NOLVADEX is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. Data are insufficient to predict which women are most likely to benefit and to determine if NOLVADEX provides any benefit in women with tumors less than 1 cm.

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 estrogen and progesterone receptor values may help to predict whether adjuvant NOLVADEX therapy is likely to be beneficial.

Reduction in Breast Cancer Incidence in High Risk Women: NOLVADEX is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent of the participants received drug for 5 years. The longer term effects are not known. In this study, there was no impact of tamoxifen on overall or breast cancer-related mortality.

NOLVADEX is indicated only for high-risk women. "High risk" is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer $\geq$ 1.67%, as calculated by the Gail model.

Examples of combinations of factors predicting a 5-year risk $\geq$ 1.67% are:

Age 35 or older and any of the following combination of factors:

- One first degree relative with a history of breast cancer, two or more benign biopsies, and a history of a breast biopsy showing atypical hyperplasia; or
- At least two first degree relatives with a history of breast cancer, and a personal history of at least one breast biopsy; or
- LCIS

Age 40 or older and any of the following combination of factors:

- One first degree relative with a history of breast cancer, two or more benign biopsies, age at first live birth 25 or older, and age at menarche 11 or younger; or
- At least two first degree relatives with a history of breast cancer, and age at first live birth 19 or younger; or
- One first degree relative with a history of breast cancer, and a personal history of a breast biopsy showing atypical hyperplasia.

Age 45 or older and any of the following combination of factors:

- At least two first degree relatives with history of breast cancer and age at first live birth 24 or younger; or

- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, age at menarche 11 or less and age at first live birth 20 or more.

Age 50 or older and any of the following combination of factors:

- At least two first degree relatives with a history of breast cancer; or
- History of one breast biopsy showing atypical hyperplasia, and age at first live birth 30 or older and age at menarche 11 or less; or
- History of at least two breast biopsies with a history of atypical hyperplasia, and age at first live birth 30 or more.

Age 55 and any of the following combination of factors:

- One first degree relative with a history of breast cancer with a personal history of a benign breast biopsy, and age at menarche 11 or less; or
- History of at least two breast biopsies with a history of atypical hyperplasia, and age at first live birth 20 or older.

Age 60 or older and:

- 5 year predicted risk of breast cancer 1.67%, as calculated by the Gail Model.

For women whose risk factors are not described in the above examples, the Gail Model is necessary to estimate absolute breast cancer risk. Health Care Professionals can obtain a Gail Model Risk Assessment Tool by dialing 1-800-456-3669 (Ext. 3838).

There are no data available regarding the effect of NOLVADEX on breast cancer incidence in women with inherited mutations (BRCA1, BRCA2).

After an assessment of the risk of developing breast cancer, the decision regarding therapy with NOLVADEX for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of NOLVADEX therapy. In the NSABP P-1 trial, NOLVADEX treatment lowered the risk of developing breast cancer during the follow-up period of the trial, but did not eliminate breast cancer risk (See Table 2 in **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

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

Reduction in Breast Cancer Incidence In High Risk Women: NOLVADEX is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus.

WARNINGS

Effects in Metastatic Breast Cancer Patients: 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.

Effects on the Uterus-Endometrial Cancer: As with other additive hormonal therapy (estrogens), an increased incidence of endometrial cancer has been reported in association with NOLVADEX treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of NOLVADEX. Any patients receiving or having previously received NOLVADEX, who report abnormal vaginal bleeding should be promptly evaluated. Patients receiving or having previously received NOLVADEX should have routine gynecological care and they should promptly inform their physician if they experience any abnormal gynecological symptoms, e.g., menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure.

In a large randomized trial in Sweden of adjuvant NOLVADEX 40 mg/day for 2-5 years, an increased incidence of uterine cancer was noted. Twenty three of 1,372 patients randomized to receive NOLVADEX versus 4 of 1,357 patients randomized to the observation group developed cancer of the uterus [RR = 5.6 (1.9-16.2), p<.001]. One of the patients with cancer of the uterus who was randomized to receive NOLVADEX never took the drug. After approximately 6.8 years of follow-up in the NSABP B-14 trial, 15 of 1,419 women randomized to receive NOLVADEX 20 mg/day for 5 years developed uterine cancer and 2 of the 1,424 women randomized to receive placebo, who subsequently were treated with NOLVADEX, also developed uterine cancer. Most of the uterine cancers were diagnosed at an early stage, but deaths from uterine cancer have been reported.

In the NSABP P-1 trial, among participants randomized to NOLVADEX there was a statistically significant increase in the incidence of endometrial cancer (33 cases of invasive endometrial cancer, compared to 14 cases among participants randomized to placebo (RR 2.48, 95% CI 1.27-4.92). This increase was primarily observed among women at least 50 years of age at the time of randomization (26 cases of invasive endometrial cancer, compared to 6 cases among participants randomized to placebo (RR 4.50, 95% CI 1.78-13.16). Among women ≤ 49 years of age at the time of randomization there were 7 cases of invasive endometrial cancer, compared to 8 cases among participants randomized to placebo (RR 0.94, 95% CI 0.28-2.89). If age at the time of diagnosis is considered, there were 4 cases of endometrial cancer among participants ≤ 49 randomized to NOLVADEX compared to 2 among participants randomized to placebo (RR 2.21, 95% CI 0.4-12.0). For women ≥ 50 at the time of diagnosis, there were 29 cases among participants randomized to NOLVADEX compared to 12 among women on placebo (RR 2.5, 95% CI 1.3-4.9). The risk ratios were similar in the two groups, although fewer events occurred in younger women. Most (29 of 33 cases in the NOLVADEX group) endometrial cancers were diagnosed in symptomatic women; although 5 of 33 cases in the NOLVADEX group occurred in asymptomatic women. Among women receiving NOLVADEX the events appeared between 1 and 61 months (average=32 months) from the start of treatment.

Among participants receiving NOLVADEX, there were 33 cases of FIGO stage I [20 IA, 12 IB, and 1 IC] endometrial cancer. Among participants receiving placebo, there were 13 FIGO stage I cases [8 IA and 5 IB]. There was a single FIGO Stage IV endometrial cancer in a participant receiving placebo. (See Table 2 in CLINICAL PHARMACOLOGY). The distribution of FIGO stage was similar between participants receiving NOLVADEX and placebo. Five women receiving NOLVADEX and 1 receiving placebo with FIGO Stage IB disease received postoperative radiation therapy in addition to surgery.

Endometrial sampling did not alter the endometrial cancer detection rate compared to women who did not undergo endometrial sampling (0.6% with sampling, 0.5% without sampling) for women with an intact uterus. There are no data to suggest that routine endometrial sampling in asymptomatic women taking NOLVADEX to reduce the incidence of breast cancer would be beneficial.

Non-Malignant Effects on the Uterus: An increased incidence of endometrial changes including hyperplasia and polyps have been reported in association with NOLVADEX treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of NOLVADEX.

There have been a few reports of endometriosis and uterine fibroids in women receiving NOLVADEX. The underlying mechanism may be due to the partial estrogenic effect of NOLVADEX. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with NOLVADEX.

Thromboembolic Effects of NOLVADEX: For treatment of breast cancer, the risks and benefits of NOLVADEX should be carefully considered in women with a history of thromboembolic events.

Data from the P-1 trial show that participants receiving NOLVADEX without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18-Nolvadex, 6-placebo, RR=3.01, 95% CI: 1.15- 9.27). Three of the pulmonary emboli, all in the NOLVADEX arm, were fatal. Eighty-seven percent of the cases of pulmonary embolism occurred in women at least 50 years of age at randomization. Among women receiving NOLVADEX, the events appeared between 2 and 60 months (average=27 months) from the start of treatment.

In this same population, a non-statistically significant increase in deep vein thrombosis (DVT) was seen in the NOLVADEX group (30-NOLVADEX, 19-placebo; RR=1.59, 95% CI: 0.86-2.98). The same increase in relative risk was seen in women $\leq$ 49 and in women $\geq$ 50, although fewer events occurred in younger women. Women with thromboembolic events were at risk for a second related event (7 out of 25 women on placebo, 5 out of 48 women on NOLVADEX) and were at risk for complications of the event and its treatment (0/25 on placebo, 4/48 on NOLVADEX). Among women receiving NOLVADEX, deep vein thrombosis events occurred between 2 and 57 months (average=19 months) from the start of treatment.

There was a non-statistically significant increase in stroke among patients randomized to NOLVADEX (24- Placebo; 34-NOLVADEX; RR 1.42; 95% CI 0.82-2.51). Six of the 24 strokes in the placebo group were considered hemorrhagic in origin and 10 of the 34 strokes in the NOLVADEX group were categorized as hemorrhagic. Seventeen of the 34 stokes in the NOLVADEX group were considered occlusive and 7 were considered to be of unknown etiology. Fourteen of the 24 strokes on the placebo arm were reported to be occlusive and 4 of unknown etiology. Among these strokes 3 strokes in the placebo group and 4 strokes in the NOLVADEX group were fatal. Eighty-eight percent of the strokes occurred in women at least 50 years of age at the time of randomization. Among women receiving NOLVADEX, the events occurred between 1 and 63 months (average=30 months) from the start of treatment.

Effects on the liver: Liver cancer: In the Swedish trial using adjuvant NOLVADEX 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the NOLVADEX-treated group versus 1 case in

the observation group (See PRECAUTIONS-Carcinogenesis). In other clinical trials evaluating NOLVADEX, no cases of liver cancer have been reported to date.

No cases of liver cancer were reported in NSABP P-1 with a median follow-up of 4.2 years.

Effects on the liver: Non-malignant effects: NOLVADEX has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included fatalities. In most reported cases the relationship to NOLVADEX is uncertain. However, some positive rechallenges and dechallenges have been reported.

In the NSABP P-1 trial, few grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on NOLVADEX). Serum lipids were not systematically collected.

Other cancers: A number of second primary tumors, occurring at sites other than the endometrium, have been reported following the treatment of breast cancer with NOLVADEX in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (non-uterine) cancers among patients receiving NOLVADEX. Whether an increased risk for other (non-uterine) cancers is associated with NOLVADEX is still uncertain and continues to be evaluated.

Effects on the Eye: Ocular disturbances, including corneal changes, cataracts, the need for cataract surgery, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving NOLVADEX.

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540 NOLVADEX; 483 placebo; RR=1.13, 95% CI 1.00-1.28) was observed. Among these same women, NOLVADEX was associated with an increased risk of having cataract surgery (101 NOLVADEX; 63 placebo; RR=1.62, 95% CI 1.17-2.25). (See Table 2 in **CLINICAL PHARMACOLOGY**) Among all women on the trial (with or without cataracts at baseline), NOLVADEX was associated with an increased risk of having cataract surgery (201 NOLVADEX; 129 placebo; RR=1.51, 95% CI 1.21-1.89). Eye examinations were not required during the study. No other conclusions regarding non-cataract ophthalmic events can be made.

Pregnancy Category D: NOLVADEX may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking NOLVADEX and should use barrier or nonhormonal contraceptive measures if sexually active. 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 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 when compared to historical controls. 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.

In rodent models of fetal reproductive tract development, tamoxifen (at doses 0.3 to 2.4-fold the human maximum recommended dose on a mg/m^2 basis) caused changes in both sexes that are similar to those caused by estradiol, ethynylestradiol and diethylstilbestrol. Although the clinical relevance of these changes is unknown, some of these changes, especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilbestrol in utero and who have a 1 in 1000 risk of developing clear-cell adenocarcinoma of the vagina or cervix. To date, in utero exposure to tamoxifen has not been shown to cause vaginal adenosis, or clear-cell adenocarcinoma of the vagina or cervix, in young women. However, only a small number of young women have been exposed to tamoxifen in utero, and a smaller number have been followed long enough (to age 15-20) to determine whether vaginal or cervical neoplasia could occur as a result of this exposure.

There are no adequate and well controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long term risk of a DES-like syndrome.

Reduction in Breast Cancer Incidence In High Risk Women - Pregnancy Category D: For sexually active women of child-bearing potential, NOLVADEX therapy should be initiated during menstruation. In women with menstrual irregularity, a negative B-HCG immediately prior to the initiation of therapy is sufficient. (See **PRECAUTIONS-Information for Patients - Reduction in Breast Cancer Incidence in High Risk Women**).

PRECAUTIONS

General: Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to NOLVADEX therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving NOLVADEX; this can sometimes be severe.

In the NSABP P-1 trial, 6 women on NOLVADEX and 2 on placebo experienced grade 3-4 drops in platelet counts (≤50, 000^3/mm).

Information for Patients:

Reduction in Breast Cancer Incidence In High Risk Women: Women who are at high risk for breast cancer can consider taking NOLVADEX therapy to reduce the incidence of breast cancer. Whether the benefits of treatment are considered to outweigh the risks depends on a woman's personal health history and on how she weighs the benefits and risks. NOLVADEX therapy to reduce the incidence of breast cancer may therefore not be appropriate for all women at high risk for breast cancer. Women who are considering NOLVADEX therapy should consult their health care professional for an assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer incidence. (See Table 2 in the CLINICAL PHARMACOLOGY) Women should understand that NOLVADEX reduces the incidence of breast cancer, but may not eliminate risk. NOLVADEX decreased the incidence of small estrogen receptor positive tumors, but did not alter the incidence of estrogen receptor negative tumors or larger tumors. In women with breast cancer who are at high risk of developing a second breast cancer, treatment with about 5 years of NOLVADEX reduced the annual incidence rate of a second breast cancer by approximately 50%.

Women who are pregnant or who plan to become pregnant should not take NOLVADEX to reduce her risk of breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking NOLVADEX if they are sexually active. For sexually active women of child-bearing potential, NOLVADEX therapy should be initiated during menstruation. In women with menstrual irregularity, a negative B-HCG immediately prior to the initiation of therapy is sufficient.(See **WARNINGS-Pregnancy Category D**.)

Two European trials of tamoxifen to reduce the risk of breast cancer were conducted and showed no difference in the number of breast cancer cases between the tamoxifen and placebo arms. These studies had

trial designs that differed from that of NSABP P-1, were smaller than NSABP P-1, and enrolled women at a lower risk for breast cancer than those in P-1.

Monitoring During NOLVADEX Therapy: Women taking or having previously taken NOLVADEX should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take NOLVADEX.

Women taking NOLVADEX to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice. Women taking NOLVADEX as adjuvant breast cancer therapy should follow the same monitoring procedures as for women taking NOLVADEX for the reduction in the incidence of breast cancer. Women taking NOLVADEX as treatment for metastatic breast cancer should review this monitoring plan with their care provider and select the appropriate modalities and schedule of evaluation.

Laboratory Tests: Periodic complete blood counts, including platelet counts, and periodic liver function tests should be obtained.

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.

In the NSABP P-1 trial, women who required coumarin-type anticoagulats for any reason were ineligible for participation in the trial. (See CONTRAINDICATIONS).

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with NOLVADEX.

Tamoxifen, N-desmethyl tamoxifen and 4-hydroxytamoxifen have been found to be potent inhibitors of hepatic cytochrome p-450 mixed function oxidases. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation, is not known.

One patient receiving NOLVADEX with concomitant phenobarbital exhibited a steady state serum level of tamoxifen lower than that observed for other patients (i.e., 26 ng/mL vs. mean value of 122 ng/mL). However, the clinical significance of this finding is not known.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

Drug/Laboratory Testing Interactions: During postmarketing surveillance, T_4 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 (doses of 5, 20, and 35 mg/kg/day for up to 2 years) revealed hepatocellular carcinoma at all doses, and the incidence of these tumors was significantly greater among rats given 20 or 35 mg/kg/day (69%) than those given 5 mg/kg/day (14%). The incidence of these tumors in rats given 5 mg/kg/day (29.5 mg/m^2) was significantly greater than in controls.

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. (See WARNINGS)

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: Although no genotoxic potential was found in a conventional battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present, increased levels of DNA adducts have been found in the livers of rats exposed to tamoxifen. Tamoxifen also has been found

to increase levels of micronucleus formation in vitro in human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

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.

Pediatric Use: The safety and efficacy of NOLVADEX in pediatric patients have not been established.

Geriatric Use: In the NSABP P-1 trial, the percentage of women at least 65 years of age was 16%. Women at least 70 years of age accounted for 6% of the participants. A reduction in breast cancer incidence was seen among participants in each of the subsets; A total of 28 and 10 invasive breast cancers were seen among participants 65 and older in the placebo and NOLVADEX groups, respectively. Across all other outcomes, the results in this subset reflect the results observed in the subset of women at least 50 years of age. No overall differences in tolerability were observed between older and younger patients. (See **CLINICAL PHARMACOLOGY - Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women** section).

ADVERSE REACTIONS

Adverse reactions to NOLVADEX are relatively mild and rarely severe enough to require discontinuation of treatment in breast cancer patients.

Continued clinical studies have resulted in further information which better indicates the incidence of adverse reactions with NOLVADEX as compared to placebo.

Metastatic Breast Cancer: 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.

In patients treated with NOLVADEX for metastatic breast cancer, the most frequent adverse reaction to NOLVADEX is hot flashes.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness, headache, hair thinning and/or partial hair loss, and vaginal dryness.

Premenopausal Women: 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 % of Women	OVARIAN ABLATION All Effects % of Women
Adverse Reactions*	n = 104 %	n = 100 %
Flush	33	46
Amenorrhea	16	69
Altered Menses	13	5
Oligomenorrhea	9	1
Bone Pain	6	6
Menstrual Disorder	6	4
Nausea	5	4
Cough/Coughing	4	1
Edema	4	1
Fatigue	4	1
Musculoskeletal Pain	3	0
Pain	3	4
Ovarian Cyst(s)	3	2
Depression	2	2
Abdominal Cramps	1	2
Anorexia	1	2

*Some women had more than one adverse reaction.

Male Breast Cancer: NOLVADEX is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of NOLVADEX in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

Adjuvant Breast Cancer: In the NSABP B-14 study, women with axillary node-negative breast cancer were randomized to 5 years of NOLVADEX 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of approximately 6.8 years) showing adverse

events more common on NOLVADEX than on placebo. The incidence of hot flashes (64% v 48%), vaginal discharge (30% v 15%), and irregular menses (25% v 19%) were higher with NOLVADEX compared with placebo. All other adverse effects occurred with similar frequency in the two treatment groups, with the exception of thrombotic events, a higher incidence was seen in NOLVADEX-treated patients (through 5 years, 1.7% versus 0.4%). Two of the patients treated with NOLVADEX who had thrombotic events died.

NSABP B-14 Study

Adverse Effect	% of Women NOLVADEX (n=1422)	Placebo (n=1437)
Hot Flashes	64	48
Fluid Retention	32	30
Vaginal Discharge	30	15
Nausea	26	24
Irregular Menses	25	19
Weight Loss (>5%)	23	18
Skin Changes	19	15
Increased SGOT	5	3
Increased Bilirubin	2	1
Increased Creatinine	2	1
Thrombocytopenia*	2	1
Thrombotic Events		
Deep Vein Thrombosis	0.8	0.2
Pulmonary Embolism	0.5	0.2
Superficial Phlebitis	0.4	0.0

*Defined as a platelet count of <100,000/mm^3

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, NOLVADEX or placebo was administered for 2 years to women 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 groups with the exception of thrombocytopenia where the incidence for NOLVADEX was 10% versus 3% for placebo, an observation of borderline statistical significance.

In other adjuvant studies, Toronto and NOLVADEX Adjuvant Trial Organization (NATO), women received either NOLVADEX or no therapy. In the Toronto study, hot flashes were observed in 29% of patients, for NOLVADEX versus 1% in the untreated group. In the NATO trial, hot flashes and vaginal

bleeding were reported in 2.8%, and 2.0% of women, respectively, for NOLVADEX versus 0.2% for each in the untreated group.

Reduction in Breast Cancer Incidence In High Risk Women: In the NSABP P-1 Trial**,** there was an increase in five serious adverse effects in the NOLVADEX group: endometrial cancer (33 cases in the NOLVADEX group versus 14 in the placebo group); pulmonary embolism (18 cases in the NOLVADEX group versus 6 in the placebo group); deep vein thrombosis (30 cases in the NOLVADEX group versus 19 in the placebo group); stroke (34 cases in the NOLVADEX group versus 24 in the placebo group); cataract formation (540 cases in the NOLVADEX group versus 483 in the placebo group) and cataract surgery (101 cases in the NOLVADEX group versus 63 in the placebo group). (See **WARNINGS** and Table 2 in **CLINICAL PHARMACOLOGY)**

The following table presents the adverse events observed in NSABP P-1 by treatment arm. Only adverse events more common on NOLVADEX than placebo are shown.

NSABP P-1 Trial: All Adverse Events

	% of Women	
	NOLVADEX N=6681	PLACEBO N=6707
Self Reported Symptoms	N=6441[1]	N=6469[1]
Hot Flashes	80	68
Vaginal Discharges	55	35
Vaginal Bleeding	23	22
Laboratory Abnormalities	N=6520[2]	N=6535[2]
Platelets decreased	0.7	0.3
Adverse Effects	N=6492[3]	N=6484[3]
Other Toxicities		
Mood	11.6	10.8
Infection/Sepsis	6.0	5.1
Constipation	4.4	3.2
Alopecia	5.2	4.4
Skin	5.6	4.7
Allergy	2.5	2.1

[1]Number with Quality of Life Questionnaires
[2]Number with Treatment Follow-up Forms
[3]Number with Adverse Drug Reaction Forms

In the NSABP P-1 trial, 15.0% and 9.7% of participants receiving NOLVADEX and placebo therapy, respectively withdrew from the trial for medical reasons. The following are the medical reasons

for withdrawing from NOLVADEX and placebo therapy, respectively: Hot flashes (3.1% vs. 1.5%) and Vaginal Discharge (0.5% vs. 0.1%).

In the NSABP P-1 trial, 8.7 percent and 9.6 percent of participants receiving NOLVADEX and placebo therapy, respectively withdrew for non-medical reasons.

On the NSABP P-1 trial, hot flashes of any severity occurred in 68% of women on placebo and in 80% of women on NOLVADEX. Severe hot flashes occurred in 28% of women on placebo and 45% of women on NOLVADEX. Vaginal discharge occurred in 35% and 55% of women on placebo and NOLVADEX respectively; and was severe in 4.5% and 12.3% respectively. There was no difference in the incidence of vaginal bleeding between treatment arms."

Postmarketing experience: 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. Very rare reports of erythema multiforme, Stevens-Johnson syndrome and bullous pemphigoid have been reported with NOLVADEX therapy.

OVERDOSAGE

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3-5 days of beginning NOLVADEX and cleared within 2-5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of NOLVADEX given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of NOLVADEX given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal

loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the NSABP B-14 adjuvant study in women with node-negative breast cancer, one 10 mg NOLVADEX tablet was given twice a day for at least five years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see CLINICAL PHARMACOLOGY). In the EBCTCG 1995 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for about 5 years than in those that used tamoxifen for a shorter period of therapy. There was no indication that doses greater than 20 mg per day were more effective. Current data from clinical trials support five years of adjuvant NOLVADEX therapy for patients with breast cancer.

Reduction in Breast Cancer Incidence In High Risk Women: The recommended dose is NOLVADEX 20 mg daily for five years. There are no data to support the use of NOLVADEX other than for 5 years. (See **CLINICAL PHARMACOLOGY-Clinical Studies - Reduction in Breast Cancer Incidence in High Risk Women**.)

HOW SUPPLIED

10 mg 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. NDC 0310-0600.

20 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 20 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 30 tablets. NDC 0310-0604.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Dispense in a well-closed, light-resistant container.

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