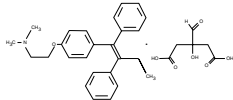


DRUGS-ABOUT.COM
TAMOXIFEN CITRATE TABLETS USP
Rx only

WARNING
For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer
 Serious and life-threatening events associated with tamoxifen in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism. Incidence rates for these events were estimated from the NSABP P-1 trial (see **CLINICAL PHARMACOLOGY, Clinical Studies, Reduction in Breast Cancer Incidence in High Risk Women**). Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for tamoxifen vs. 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women-years of 0.17 for tamoxifen vs. 0.04 for placebo). For stroke, the incidence rate per 10,000 women-years was 1.43 for tamoxifen vs. 1.00 for placebo. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for tamoxifen versus 0.25 for placebo. Some of the strokes, pulmonary emboli, and uterine malignancies were fatal. Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering tamoxifen to reduce their risk of developing breast cancer. The benefits of tamoxifen outweigh its risks in women already diagnosed with breast cancer.

Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma
 * Updated long-term follow-up data (median length of follow-up is 6.9 years) from NSABP P-1 study. See **WARNINGS, Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma**.
 ** See Table 3 under **CLINICAL PHARMACOLOGY, Clinical Studies**.

DESCRIPTION
 Tamoxifen citrate tablets USP, a nonsteroidal antiestrogen, are for oral administration. Tamoxifen citrate tablets are available as: **10 mg Tablets**. Each tablet contains 15.2 mg of tamoxifen citrate which is equivalent to 10 mg of tamoxifen. Each tablet contains 30.4 mg of tamoxifen citrate which is equivalent to 20 mg of tamoxifen. 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 3 months are 122 ng/mL and 371 ng/mL, respectively. After initiation of therapy with tamoxifen, 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 steady-state, crossover study of 10 mg tamoxifen tablets given twice a day vs. a 20 mg tamoxifen tablet given once daily, the 20 mg tamoxifen tablet was bioequivalent to the 10 mg tamoxifen tablets.



$C_{26}H_{29}NO_2 \cdot C_6H_8O_7$ M.W. 563.64
 Tamoxifen citrate has a pK_a of 8.85 and 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
 Tamoxifen citrate 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 antitumor effects by binding the estrogen receptors. In cytotoxic derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

Absorption and Distribution
 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 about 5 to 7 days. The average steady-state plasma concentration of *N*-desmethyl tamoxifen is 15 ng/mL (range 10 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 3 months are 122 ng/mL and 371 ng/mL, respectively. After initiation of therapy with tamoxifen, 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 steady-state, crossover study of 10 mg tamoxifen tablets given twice a day vs. a 20 mg tamoxifen tablet given once daily, the 20 mg tamoxifen tablet was bioequivalent to the 10 mg tamoxifen tablets.

Metabolism
 Tamoxifen is extensively metabolized after oral administration. *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. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

Excretion
 Studies in women receiving 20 mg of ¹⁴C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as 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.

Special Populations
 The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

Pediatric patients: Approved labeling describing pediatric pharmacokinetic information obtained from patients with McCune-Albright syndrome is available for AstraZeneca's tamoxifen citrate tablets. However, due to AstraZeneca's marketing exclusivity rights, this drug product is not labeled for pediatric use. The long-term effects of tamoxifen therapy in girls have not been established. In adults treated with tamoxifen citrate an increase in the incidence of endometrial adenocarcinoma and uterine sarcoma has been noted (see **BOXED WARNING**).

Drug-Drug Interactions
In vitro studies showed that erythromycin, cyclosporine, nifedipine and diltiazem competitively inhibited formation of *N*-desmethyl tamoxifen with apparent K_i of 20, 1, 45 and 30 μM, respectively. The clinical significance of these *in vitro* studies is unknown. Tamoxifen reduced the intracellular concentration of tamoxifen by 37% without effects on IC_{50} and IC_{90} in the presence of tamoxifen. Ritalin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC and C_{max} by 86% and 55%, respectively. Aminoglutethimide reduces tamoxifen and *N*-desmethyl tamoxifen plasma concentrations. Metyroloproprone reduces plasma concentrations of *N*-desmethyl, but not tamoxifen.

Clinical Studies - Metastatic Breast Cancer
Premenopausal Women (Tamoxifen Citrate vs. Aritranch)
 Three prospective, randomized studies (Ingle, Pritchard, Buchanan) compared tamoxifen to ovarian ablation (oophorectomy or ovarian irradiation) in premenopausal women with advanced breast cancer. Although the objective response rate, time to treatment failure, and quality of life were similar with both treatments, the limited patient accrual precluded a demonstration of equivalence. In an overview analysis of survival data from the 3 studies, the hazard ratio for death (tamoxifen/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 tamoxifen, 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 tamoxifen 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 tamoxifen have shown that tamoxifen is effective for the palliative treatment of male breast cancer. Sixty-six of these 132 evaluable patients responded to tamoxifen 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 tamoxifen using doses of 20-40 mg/day for 1-5 years. Twenty-five percent of patients received 1 year or less of total 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/mg), and 31% were ER unknown. Among 29,441 patients with ER positive or unknown breast cancer, 56% were entered into trials comparing tamoxifen to no adjuvant therapy and 42% were entered into trials comparing tamoxifen 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 tamoxifen vs. 50.5% for control (logrank $Z_p < 0.00001$). The recurrence-free rate at 10 years was 59.7% for tamoxifen vs. 44.5% for control (logrank $Z_p < 0.00001$). 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 78.3% for tamoxifen vs. 73.2% for control (logrank $Z_p < 0.00001$). The recurrence-free rate at 10 years was 79.2% for tamoxifen versus 64.3% for control (logrank $Z_p < 0.00001$). 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 tamoxifen, the proportional reductions in mortality were 12%, 17% and 26%, respectively (trend significant at $Z_p < 0.035$). The corresponding reductions in breast cancer recurrence were 21%, 29% and 47% (trend significant at $Z_p < 0.0001$). Benefit is less clear for women with ER poor breast cancer in whom the proportional reduction in recurrence was 10% ($Z_p < 0.07$) for durations taken together, or 9% ($Z_p < 0.27$) for durations taken separately. The corresponding reduction in mortality was 6% (NS). The effects of about 5 years of tamoxifen 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.

Note Positive - Individual Studies
 Two studies (Huy 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 tamoxifen was added to adjuvant cytotoxic chemotherapy. In the Huy study, tamoxifen was added to "low-dose" CMF (cyclophosphamide, methotrexate and fluorouracil). In the NSABP B-09 study, tamoxifen was added to methiphan [1-phenylalanine methyl ester (P)] (Aronson).
 In the Huy study, patients with a positive (more than 3 fmo) 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 a benefit 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 tamoxifen without any clear relationship to estrogen or progesterone 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 tamoxifen 20 mg/day for 5 years vs. placebo and were disease-free at the end of this 5-year period were offered randomization to an additional 5 years of tamoxifen for placebo. With 4 years of follow-up after this randomization, 92% of the women that received 5 years of tamoxifen were alive and disease-free, compared to 86% of the women scheduled to receive 10 years of tamoxifen ($p < 0.003$). Overall survival was 96% and 94%, respectively ($p = 0.08$). Results of the B-14 study suggest that continuation of therapy beyond 5 years does not provide additional benefit.
 A Scottish trial of 5 years of tamoxifen vs. 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 tamoxifen 40 mg/day for 2 or 5 years, overall survival at 10 years was estimated to be 80% in the patients in the 5-year tamoxifen group, compared with 74% among corresponding patients in the 2-year tamoxifen group ($p < 0.03$). Disease-free survival at 10 years was 73% in the 5-year group and 67% in the 2-year group ($p = 0.009$). Compared with 2 years of tamoxifen treatment, 5 years of treatment resulted in a slightly greater reduction in the incidence of contralateral breast cancer at 10 years, but this difference was not statistically significant.

Contraindications
Contraindications - Ductal Carcinoma in Situ
 The incidence of contralateral breast cancer is reduced in breast cancer patients (premenopausal and postmenopausal) receiving tamoxifen 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 tamoxifen 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 tamoxifen were 13% (NS), 26% ($Z_p < 0.004$) and 47% ($Z_p < 0.00001$), with a significant trend favoring longer tamoxifen duration ($Z_p = 0.008$). The proportional reductions in the incidence of contralateral breast cancer were independent of age and ER status of the primary tumor. Treatment with about 5 years of tamoxifen 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 tamoxifen 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 tamoxifen 20 mg/day for 5 years vs. 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 1,000 patients in the placebo group compared with 5.0 per 1,000 patients in the tamoxifen group, at 10 years after first randomization.

Clinical Studies - Ductal Carcinoma in Situ
NSABP B-24, a double-blind, randomized trial included women with ductal carcinoma in situ (DCIS). This trial compared the addition of tamoxifen or placebo to treatment with lumpectomy and radiation therapy for women with DCIS. The primary objective was to determine whether 5 years of tamoxifen therapy (20 mg/day) would reduce the incidence of invasive breast cancer in the ipsilateral (the same) or contralateral (the opposite) breast.
 In this trial 1,804 women were randomized to receive either tamoxifen or placebo for 5 years: 902 women were randomized to tamoxifen 10 mg tablets twice a day and 902 women were randomized to placebo. As of December 31, 1998, follow-up data were available for 1,738 women and the median duration of follow-up was 74 months.
 The tamoxifen and placebo groups were well balanced for baseline demographic and prognostic factors. Over 80% of the tumors were less than or equal to 1 cm in their maximum dimension, were not palpable, and were detected by mammography alone. Over 60% of the study population was postmenopausal. In 16% of patients, the margin of the resected specimen was reported as being positive after surgery. Approximately half of the tumors were reported to contain comedo type DCIS.
 For the primary endpoint, the incidence of invasive breast cancer was reduced by 43% among women assigned to tamoxifen (44 cases - tamoxifen, 74 cases - placebo; $p = 0.004$; relative risk (RR)=0.57, 95% CI: 0.39-0.84). No data are available regarding the ER status of the invasive cancers. The stage distribution of the invasive cancers was similar to that reported usually in the SEER data base. Results are shown in Table 1. For each endpoint the following results are presented: the number of events and rate per 1,000 women per year for the placebo and tamoxifen groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between tamoxifen and placebo. Relative risks less than 1.0 indicate a benefit of tamoxifen therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits of tamoxifen therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists.

Type of Event	Lumpectomy, radiotherapy, and placebo		Lumpectomy, radiotherapy, and tamoxifen		RR	95% CI limits
	No. of events	Rate per 1000 women per year	No. of events	Rate per 1000 women per year		
Invasive breast cancer (Primary endpoint)	74	16.73	44	9.60	0.57	0.39 to 0.84
- Ipsilateral	47	10.61	27	5.90	0.56	0.33 to 0.91
- Contralateral	25	5.64	17	3.71	0.66	0.33 to 1.27
- Side undetermined	2	-	0	-	-	-
Secondary Endpoints						
DCIS	58	12.66	41	8.95	0.71	0.46 to 1.08
- Ipsilateral	46	10.40	38	8.29	0.88	0.51 to 1.25
- Contralateral	10	2.26	3	0.65	0.29	0.05 to 1.13
All Breast Cancer Events	129	29.16	84	18.34	0.63	0.47 to 0.83
All ipsilateral events	96	21.70	65	14.19	0.65	0.47 to 0.91
All contralateral events	37	8.36	20	4.37	0.52	0.29 to 0.92
Deaths	32	-	28	-	-	-
Uterine Malignancies ¹	4	-	9	-	-	-
Endometrial Adenocarcinoma ¹	4	0.57	8	1.15	-	-
Uterine Sarcoma ¹	0	0.0	1	0.14	-	-
Second primary malignancies (other than endometrial and breast)	30	-	29	-	-	-
Stroke	2	-	7	-	-	-
Thromboembolic events (DVT, PE)	5	-	15	-	-	-

Survival was similar in the placebo and tamoxifen groups. At 5 years from study entry, survival was 97% for both groups.
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 5 years of tamoxifen (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 tamoxifen, 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 tamoxifen or placebo for five years. The median duration of treatment was 3.5 years. As of January 31, 1998, follow-up data are available for 13,114 women. Twenty-seven percent of women randomized to placebo (1782) and 24% of women randomized to tamoxifen (1596) completed 5 years of therapy. The demographic characteristics of women on the trial with follow-up data are shown in Table 2.

Characteristic	Placebo		Tamoxifen	
	#	%	#	%
Age (yrs.)				
≤ 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	555	8	510	8
≤ 11	1,717	26	1,764	27
# of first degree relatives with breast cancer				
0	1,584	24	1,525	23
1	3,744	57	3,744	57
2 ¹	1,272	19	1,275	20
Prior hysterectomy				
No	4,173	63.5	4,018	62.4
Yes	2,397	36.5	2,463	37.7
# of previous breast biopsies				
0	2,935	45	2,944	45
1	1,833	28	1,850	28
≥ 2	1,802	27	1,771	27
History of atypical hyperplasia in the breast				
No	9,569	91	9,569	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 3. After a median follow-up of 4.2 years, the incidence of invasive breast cancer was reduced by 44% among women assigned to tamoxifen (86 cases-tamoxifen, 156 cases-placebo; $p < 0.0001$; relative risk (RR)=0.56, 95% CI: 0.43-0.72). A reduction in the incidence of breast cancer was seen in each of the following subgroups: women with ER positive or unknown or without LCIS, and in each of the absolute risk levels specified in Table 3. A non-significant decrease in the incidence of ductal carcinoma in situ (DCIS) was seen (23 tamoxifen, 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 tamoxifen, 59 placebo; RR=1.04, 95% CI: 0.73-1.49).
 No overall difference in the incidence of stroke was observed in the tamoxifen (19) versus placebo (19) group. No difference in breast cancer-related mortality was observed (4 deaths in tamoxifen group vs. 5 deaths in placebo group).
 Although there was a non-significant reduction in the number of hip fractures (9 on tamoxifen, 20 on placebo) in the tamoxifen group, the number of wrist fractures was similar in the two treatment groups (69 on tamoxifen, 74 on placebo). No information regarding bone mineral density or other markers of osteoporosis is available.
 The risks of tamoxifen therapy include endometrial cancer, DVT, PE, stroke, cataract formation and cataract surgery (See **Table 3**). In the NSABP P-1 trial, 33 cases of endometrial cancer were observed in the tamoxifen group vs. 14 in the placebo group (RR=2.48, 95% CI: 1.27-4.82). Deep vein thrombosis was observed in 20 women receiving tamoxifen vs. 19 in women receiving placebo (RR=1.59, 95% CI: 0.86-2.98). Eighteen cases of pulmonary embolism were observed in the tamoxifen group vs. 6 in the placebo group (RR=3.01, 95% CI: 1.15-2.27). There were 34 strokes on the tamoxifen 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 tamoxifen vs. 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 tamoxifen vs. 129 women receiving placebo (RR=1.51, 95% CI: 1.21-1.89) (See **WARNINGS**).
 Table 3 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 tamoxifen groups; and the relative risk (RR) and its associated 95% confidence interval (CI) between tamoxifen and placebo. Relative risks less than 1.0 indicate a benefit of tamoxifen therapy. The limits of the confidence intervals can be used to assess the statistical significance of the benefits or risks of tamoxifen therapy. If the upper limit of the CI is less than 1.0, then a statistically significant benefit exists.
 For most risk factors, multiple risk factors would have been required for eligibility. This table considers risk factors individually, regardless of their co-existing risk factors, for women who developed breast cancer. The 5-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**).

Type Of Event	Placebo	Rate/1000 Women/Year		RR	95% CI Limits
		Tamoxifen	Placebo		
Invasive Breast Cancer	156	86	64.9	0.56	0.43-0.72
Age ≤ 49	59	38	6.34	0.11	0.65 to 0.43-0.98
Age 50-59	46	25	6.31	0.56	0.35-0.91
Age ≥ 60	51	23	7.17	0.45	0.27-0.74
Risk Factors for Breast Cancer History, LCIS					
No	140	78	62.73	0.51	0.56 to 0.43-0.74
Yes	16	8	12.33	0.33	0.50 to 0.21-1.17
History of Atypical Hyperplasia					
No	138	84	63.7	0.89	0.61 to 0.47-0.80
Yes	18	2	8.69	0.12	0.03-0.52
No. First Degree Relatives					

tamoxifen therapy. When tamoxifen is administered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of tamoxifen should be carefully considered in women with a history of thromboembolic events. Data from the NSABP P-1 trial show that participants receiving tamoxifen without a history of pulmonary emboli (PE) had a statistically significant increase in pulmonary emboli (18-tamoxifen, 6-placebo, RR=3.01, 95% CI: 1.15- 9.27). Three of the pulmonary emboli, all in the tamoxifen arm, were fatal. Eighty-seven percent of the cases of pulmonary emboli occurred in women at least 50 years of age at randomization. Among women receiving tamoxifen, 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 tamoxifen group (30-tamoxifen, 19-placebo, RR=1.59, 95% CI: 0.82-2.98). The same increase in relative risk was seen in women <49 and in women ≥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 tamoxifen, 5 out of 48 women on placebo) and were at risk for complications of the event and its treatment (0/25 on placebo, 4/48 on tamoxifen). Among women receiving tamoxifen, 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 tamoxifen (24-Placebo, 34-tamoxifen, 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 tamoxifen group were categorized as hemorrhagic. Eleven of the 34 strokes in the tamoxifen 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 tamoxifen 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 tamoxifen, 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 tamoxifen 40 mg/day for 2-5 years, 3 cases of liver cancer have been reported in the tamoxifen-treated group vs. 1 case in the observation group (See **PRECAUTIONS, Carcinogenesis**). In other clinical trials evaluating tamoxifen, no cases of liver cancer have been reported to date.

One case of liver cancer was reported in NSABP P-1 in a participant randomized to tamoxifen.

Effects On The Liver: Non-Malignant Effects
Tamoxifen has been associated with 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 tamoxifen is uncertain. However, some positive rechallenge and dechallenge have been reported.

In the NSABP P-1 trial, low grade 3-4 changes in liver function (SGOT, SGPT, bilirubin, alkaline phosphatase) were observed (10 on placebo and 6 on tamoxifen). 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 tamoxifen in clinical trials. Data from the NSABP B-14 and P-1 studies show no increase in other (non-uterine) cancers among patients receiving tamoxifen. Whether an increased risk for other (non-uterine) cancers is associated with tamoxifen is still uncertain and continues to be evaluated.

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

In the NSABP P-1 trial, an increased risk of borderline significance of developing cataracts among those women without cataracts at baseline (540-tamoxifen; 483-placebo; RR=1.13, 95% CI: 1.00-1.28) was observed. Among these same women, tamoxifen was associated with an increased risk of having cataract surgery (101-tamoxifen; 63-placebo; RR=1.62, 95% CI: 1.17-2.25) (See **Table 3 in CLINICAL PHARMACOLOGY**). Among all women on the trial (with or without cataracts at baseline), tamoxifen was associated with an increased risk of having cataract surgery (201-tamoxifen; 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
Tamoxifen may cause fetal harm when administered to a pregnant woman. Tamoxifen should be advised not to become pregnant while taking tamoxifen or within 2 months of discontinuing tamoxifen and should use barrier or nonhormonal contraceptive measures if sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. 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, nonreproductive development was retarded and was observed. 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 with 10 mg/kg/day (about 2-fold the daily maximum recommended human dose on a mg/m² basis) 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 0.002 to 2.4-fold the daily maximum recommended human dose on a mg/m² basis) caused a decrease in the number of spermatozoa in both sexes that are similar to those caused by estradiol, ethynodiol diacetate and diethylstilbestrol. Although the clinical relevance of these changes is unknown, as in most cases 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 vitro* 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, tamoxifen 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/mm³, infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen. In one patient, a decrease in platelet counts was associated with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen; this can sometimes be severe. In the NSABP P-1 trial, 6 women on tamoxifen and 2 on placebo experienced grade 3-4 drops in platelet counts (<50,000/mm³).

Information for Patients

Reduction in Invasive Breast Cancer and DCIS in Women with DCIS
Women with DCIS treated with lumpectomy and radiation therapy who are considering tamoxifen should be aware of the incidence of a second breast cancer event should assess the risks and benefits of therapy, since treatment with tamoxifen decreased the incidence of invasive breast cancer, but has not been shown to decrease the incidence of DCIS (See **Table 1 in CLINICAL PHARMACOLOGY**).

Reduction in Breast Cancer Incidence in High Risk Women

Women who are at high risk for breast cancer can consider taking tamoxifen 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. Tamoxifen 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 tamoxifen 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 3 in CLINICAL PHARMACOLOGY**). Women should be aware that tamoxifen reduces the incidence of breast cancer, but may not eliminate it. Tamoxifen 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 tamoxifen 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 tamoxifen to reduce her risk of breast cancer. Effective non-hormonal contraception must be used by all premenopausal women taking tamoxifen and for approximately two months after discontinuing therapy if they are sexually active. Tamoxifen does not cause infertility, even in the presence of menstrual irregularity. For sexually active women of child-bearing potential, tamoxifen 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 Tamoxifen Therapy
Women taking or having previously taken tamoxifen 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 tamoxifen.

Women taking tamoxifen to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the start of therapy. These studies should be repeated at regular intervals while on therapy, or keeping with good medical practice. Women taking tamoxifen as adjuvant breast cancer therapy should follow the same monitoring procedures as for women taking tamoxifen for the reduction in the incidence of breast cancer. Women taking tamoxifen 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 tamoxifen 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 anticoagulants 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 tamoxifen. Tamoxifen reduced letrozole plasma concentrations by 37%. 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. Tamoxifen and *N*-desmethyl tamoxifen plasma concentrations have been shown to be reduced when coadministered with rifampin or aminoglutethimide. Induction of CYP3A4-mediated metabolism is considered to be the mechanism by which these reductions occur; other CYP3A4 inducing agents have not been studied to confirm this effect.

One patient receiving tamoxifen 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 of 122 ng/mL). However, the clinical significance of this finding is not known. Rifampin induced the metabolism of tamoxifen and significantly reduced the plasma concentrations of tamoxifen in 10 patients. Aminoglutethimide reduces tamoxifen and *N*-desmethyl tamoxifen plasma concentrations. Metyroxyprogesterone reduces plasma concentrations of *N*-desmethyl, but not tamoxifen.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and *N*-desmethyl tamoxifen. **Drug/Laboratory Testing Interactions**
During postmarketing surveillance, 14 elevations were reported for a few postmenopausal patients which may be explained by increases in thyroid-binding globulin. These elevations were not accompanied by increases in free thyroxine.

Variations in the karyopycnotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently seen in postmenopausal patients given tamoxifen. In the postmarketing experience with tamoxifen, infrequent cases of hyperlipidemia have been reported. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with pre-existing hyperlipidemia (see **ADVERSE REACTIONS, Postmarketing Experience** section).

Carcinogenesis
A conventional carcinogenic study in rats at doses of 5, 20, and 35 mg/kg/day (about one, three and seven-fold the daily maximum recommended human dose on a mg/m² basis) administered by oral gavage for up to 2 years revealed a significant increase in hepatocellular carcinoma at all doses. The incidence of these tumors was significantly greater among rats administered 20 or 35 mg/kg/day (69% compared to those administered 5 mg/kg/day (14%). In a separate study, rats were administered tamoxifen at 45 mg/kg/day (about nine-fold the daily maximum recommended human dose on a mg/m² basis); hepatocellular neoplasia was exhibited at 3 to 6 months. Granulosa cell ovarian tumors and interstitial cell testicular tumors were observed in two separate mouse studies. The mice were administered the trans and racemic forms of tamoxifen for 13 to 15 months at doses of 5, 20 and 50 mg/kg/day (about one-half, two and five-fold the daily recommended human dose on a mg/m² basis).

Mutagenesis
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. However, increased levels of DNA adducts were observed in CYP19 post-labelling in DNA from rat liver and cultured human lymphocytes. Tamoxifen also has been found to increase levels of micronucleus formation in *in vitro* human lymphoblastoid cell line (MCL-5). Based on these findings, tamoxifen is genotoxic in rodent and human MCL-5 cells.

Impairment of Fertility
Tamoxifen produced impairment of fertility and conception in female rats at doses of 0.04 mg/kg/day (about 0.01-fold the daily maximum recommended human dose on a mg/m² basis) when dosed for two weeks prior to mating through day 7 of pregnancy. At this dose, fertility and reproductive indices were markedly reduced with total fetal mortality. Fetal mortality was also increased at doses of 0.16 mg/kg/day (about 0.03-fold the daily maximum recommended human dose on a mg/m² basis) when female rats were dosed from days 7-17 of pregnancy. Tamoxifen produced abortion, premature delivery and death in rabbits administered doses equal to or greater than 0.125 mg/kg/day (about 0.05-fold the daily maximum recommended human dose on a mg/m² basis). There were no teratogenic changes in either rats or rabbits.

Pregnancy: Teratogenic Effect: 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 tamoxifen, 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
Approved labeling describing pediatric safety and efficacy information regarding tamoxifen use in patients with McCune-Albright syndrome is available for AstraZeneca's tamoxifen citrate tablets. However, due to AstraZeneca's marketing exclusivity rights, this drug product is not labeled for pediatric use. The long-term effects of tamoxifen therapy for girls have not been established. In adults treated with tamoxifen, an increase in incidence of endometrial adenocarcinoma and uterine sarcoma has been noted (see **BOXED WARNING**).

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 10% of the participants. A reduction in breast cancer incidence was seen among participants in each of the subsets: A total of 28 and 6% invasive breast cancers were seen among participants 65 and older in the placebo and tamoxifen 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 tamoxifen 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 tamoxifen

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 tamoxifen and generally subside rapidly. In patients treated with tamoxifen for metastatic breast cancer, the most frequent adverse reaction to tamoxifen 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 tamoxifen therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

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

*Some women had more than one adverse reaction.

Male Breast Cancer
Tamoxifen is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of tamoxifen 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 tamoxifen 20 mg/day or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of approximately 6.8 years) showing an increased risk of having cataract surgery on tamoxifen than on placebo. The incidence of hot flashes (84% vs. 45%), vaginal discharge (30% vs. 15%), and irregular menses (25% vs. 19%) were higher with tamoxifen compared with placebo. All other adverse effects occurred with similar frequency in the 2 treatment groups, with the exception of thrombotic events; a higher incidence was seen in tamoxifen-treated patients (through 5 years, 1.7% vs. 0.4%). Two of the patients treated with tamoxifen who had thrombotic events in:

Adverse Effect	NSABP B-14 Study	
	Tamoxifen (n=1422)	Placebo (n=1437)
Hot flashes	84	45
Fluid retention	34	20
Vaginal discharge	30	15
Nausea	26	24
Irregular menses	25	19
Weight loss (x%)	23	18
Skin changes	19	15
Increased SGOT	5	3
Increased bilirubin	2	1
Increased creatinine	2	1
Thrombocytopenia*	2	1
Thrombotic events	2	1
Deep vein thrombosis	0.8	0.2
pulmonary embolism	0.8	0.2
Superficial phlebitis	0.4	0.0

*Defined as a platelet count of <100,000/mm³

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, tamoxifen or placebo was administered for 2 years to women following mastectomy. When compared to placebo, tamoxifen showed a significantly higher incidence of hot flashes (19% vs. 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 tamoxifen was 10% vs. 3% for placebo, an observation of borderline statistical significance. In other adjuvant studies, Toronto and Tamoxifen Adjuvant Trial Organization (NATO), women received either tamoxifen or no therapy. In the Toronto study, hot flashes were observed in 29% of patients for tamoxifen (1% in the untreated group). In the NATO trial, hot flashes were reported in 2.8% and 2.0% of women, respectively, for tamoxifen vs. 0.2% for each in the untreated group.

Ductal Carcinoma in Situ (DCIS)
The type and frequency of adverse events in the NSABP B-24 trial were consistent with those observed in the other adjuvant trials conducted with tamoxifen.

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 tamoxifen group: endometrial cancer (33 cases in the tamoxifen group vs. 14 in the placebo group); pulmonary embolism (18 cases in the tamoxifen group vs. 6 in the placebo group); deep vein thrombosis (30 cases in the tamoxifen group vs. 19 in the placebo group); stroke (34 cases in the tamoxifen group vs. 24 in the placebo group); cataract formation (540 cases in the tamoxifen group vs. 483 in the placebo group) and cataract surgery (101 cases in the tamoxifen group vs. 63 in the placebo group). (See **WARNINGS and Table 3 in CLINICAL PHARMACOLOGY**).

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

	NSABP P-1 Trial: All Adverse Events	
	Tamoxifen N=6611	Placebo N=6707
Self Reported Symptoms	N=6441†	N=6491†
Hot flashes	80	68
Vaginal discharges	55	35
Vaginal bleeding	23	22
Laboratory Abnormalities	N=6592†	N=6552†
Platelets decreased	0.2	0.3
Adverse Effects	N=6492‡	N=6484‡
Other Toxicities		
Mood	11.6	10.8
Infection/Sepsis	6.0	5.1
Constipation	4.4	3.2
Allopecia	5.2	4.4
Skin	4.7	4.7
Allergy	2.5	2.1

† Number with Quality of Life Questionnaires
‡ Number with Treatment Follow-up Forms
§ Number with Adverse Drug Reaction Forms

In the NSABP P-1 trial, 15.0% and 9.7% of participants receiving tamoxifen and placebo therapy, respectively withdrew from the trial for medical reasons. The following are the medical reasons for withdrawing from tamoxifen 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% and 9.6% of participants receiving tamoxifen and placebo therapy, respectively withdrew for non-medical reasons.

In the NSABP P-1 trial, hot flashes of any severity occurred in 88% of women on placebo and in 80% of women on tamoxifen. Severe hot flashes occurred in 28% of women on placebo and 45% of women on tamoxifen. Vaginal discharge occurred in 35% and 55% of women on placebo and tamoxifen 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, skin rash and headaches. Usually these have not been of sufficient severity to require dose reduction or discontinuation of treatment. Very rare reports of erythema multiforme, Stevens-Johnson syndrome, bullous pemphigoid, interstitial pneumonitis, and rare reports of hypersensitivity reactions including angioedema have been reported with tamoxifen therapy. In some of these cases, the time to onset was more than one year. Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen (see **PRECAUTIONS, Drug/Laboratory Testing Interactions** section).

Pediatric Patients - McCune-Albright Syndrome: Approved labeling describing pediatric adverse reaction information regarding tamoxifen use in patients with McCune-Albright syndrome is available for AstraZeneca's tamoxifen citrate tablets. However, due to AstraZeneca's marketing exclusivity rights, this drug product is not labeled for pediatric use. The long-term effects of tamoxifen therapy for girls have not been established. Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. A causal relationship has not been established; however, as an increase in the incidence of endometrial adenocarcinoma and uterine sarcoma has been noted in adults treated with tamoxifen (see **BOXED WARNING**), continued monitoring of McCune-Albright patients treated with tamoxifen for long-term uterine effects is recommended.

OVERDOSAGE
Signs observed at the highest doses following studies to determine LD₅₀ 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 tamoxifen in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness was noted. These symptoms occurred within 3-5 days of beginning tamoxifen and cleared within 2-5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after tamoxifen was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to tamoxifen therapy is unknown. Doses given in these patients were all greater than 400 mg/m² loading dose, followed by maintenance doses of 150 mg/m² of tamoxifen 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/m² loading dose, followed by maintenance doses of 80 mg/m² of tamoxifen given twice a day. For a woman with a body surface area of 1.5 m² the minimal loading 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.

DOSEAGE 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 this single agent adjuvant studies in women, one 10 mg tamoxifen citrate 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 tamoxifen citrate tablet was given twice a day for at least 5 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 2005 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 5 years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

Ductal Carcinoma in Situ (DCIS)
The recommended dose is tamoxifen citrate tablets 20 mg daily for 5 years.

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

HOW SUPPLIED
Tamoxifen Citrate Tablets USP are available as white, round, unscored, uncoated, biconvex tablets, debossed with "X" and the figure "10" on one side and the figure "5656" on the reverse side containing 15.2 mg tamoxifen citrate in an amount equivalent to 10 mg of tamoxifen, packaged in bottles of 60, 100, 180, 500 and 1000 tablets. Tamoxifen Citrate Tablets USP are available as white, round, unscored, uncoated, biconvex tablets, debossed with "X" and the figure "20" on one side and the figure "5657" on the reverse side containing 30.4 mg tamoxifen citrate in an amount equivalent to 20 mg of tamoxifen, packaged in bottles of 100 and 500 tablets.

PHARMACIST: Dispense in a well-closed, light-resistant container as defined in the USP. Use child-resistant closure (as required). Store at controlled room temperature 15°-30°C (59°-86°F) (See USP).

Manufactured for
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Patient Information About Tamoxifen Citrate Tablets USP For Breast Cancer Treatment
and Reduction in the Incidence of Breast Cancer Tamoxifen (ta-MOX-i-len)

Please read this information carefully before you begin taking tamoxifen. It is important to read this information each time you pre- or start taking tamoxifen and each time you take a new dose. This summary does not tell you everything about tamoxifen. Your health care professional is the best source of information about this medicine. You should talk with him or her before you begin taking tamoxifen and at regular checkups. In addition, the professional package insert contains more detailed information on tamoxifen.

What Are the Most Important Things I Should Know About