PDR®

46 EDITION

1992

# PHYSICIANS' DESK REFERENCE®

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## Hollister-Stier—Cont.

**CHLO-AMINE:** As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
Patients should not drive or operate machinery after taking Chlo-Amine. Drowsiness, dizziness, blurred vision, dry mouth and gastrointestinal upsets may occur. Keep out of reach of children.
The asthmatic patient should take the chloropheniramine maleate tablets with caution.
**LIMITED WARRANTY:** A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.
The foregoing statement is made in lieu of any other warranty, express or implied, including any warranty of merchantability or fitness. Representatives of the Company are not authorized to vary the terms of this warranty or the contents of any printed labeling for this product except by printed notice from the Company's Spokane, WA office. The prescriber and user of this product must accept the terms hereof.

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**Pkgd. and Dist. by:**
Miles Inc.
Hollister-Stier
Pharmaceutical Division
Spokane, WA 99207 USA
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## ICI Pharma
**A Business Unit of ICI Americas Inc.**
**WILMINGTON, DE 19897 USA**

### NOLVADEX® 10 mg Tablets ℞
*[nol'va-dex"]*
**(tamoxifen citrate)**

### DESCRIPTION
NOLVADEX® (tamoxifen citrate) tablets for oral administration contain 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg of tamoxifen. It is a nonsteroidal antiestrogen. Chemically, NOLVADEX is the trans-isomer of a triphenylethylene derivative. The chemical name is (Z) 2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N, N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1).
Tamoxifen citrate has a molecular weight of 563.62, the pKa' is 8.85, the equilibrium solubility in water at 37°C is 0.5 mg/mL and in 0.02 N HCl at 37°C, it is 0.2 mg/mL.
NOLVADEX is intended only for oral administration; the tablets should be protected from heat and light.
Inactive ingredients: carboxymethylcellulose calcium, magnesium stearate, mannitol, starch.

### CLINICAL PHARMACOLOGY
NOLVADEX is a nonsteroidal agent which has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding to estrogen receptors.
In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein. Preliminary pharmacokinetics in women using radiolabeled tamoxifen has shown that most of the radioactivity is slowly excreted in the feces, with only small amounts appearing in urine. The drug is excreted mainly as conjugates, with unchanged drug and hydroxylated metabolites accounting for 30% of the total.
Blood levels of total radioactivity following single oral doses of approximately 0.3 mg/kg reached peak values of 0.06–0.14 μg/mL at 4–7 hours after dosing, with only 20%–30% of the drug present as tamoxifen. There was an initial half-life of 7–14 hours with secondary peaks four or more days later. The prolongation of blood levels and fecal excretion is believed to be due to enterohepatic circulation.
Two studies (Hubay and NSABP B-09) demonstrated an improved disease-free survival following radical or modified radical mastectomy in postmenopausal women or women 50 years of age or older with surgically curable breast cancer with positive axillary nodes when NOLVADEX was added to adjuvant cytotoxic chemotherapy. In the Hubay study, NOLVADEX was added to "low-dose" CMF (cyclophosphamide, methotrexate and fluorouracil). In the NSABP B-09 study, NOLVADEX was added to melphalan [L-phenylalanine mustard (P)] and fluorouracil (F).
Tumor hormone receptors may help predict which patients will benefit from the adjuvant therapy, but not all breast cancer adjuvant NOLVADEX studies have shown a clear relationship between hormone receptor status and treatment effect. In the Hubay study, patients with a positive (more than 3 fmol) estrogen receptor were more likely to benefit. In the NSABP B-09 study in women age 50–59 years, only women with both estrogen and progesterone receptor levels 10 fmol or greater clearly benefited, while there was a nonstatistically significant trend toward adverse effect in women with both estrogen and progesterone receptor levels less than 10 fmol. In women age 60–70 years, there was a trend toward a beneficial effect of NOLVADEX without any clear relationship to estrogen or progesterone receptor status.
Three prospective studies (ECOG-1178, Toronto, NATO) using NOLVADEX adjuvantly as a single agent demonstrated an improved disease-free survival following total mastectomy and axillary dissection for postmenopausal women with positive axillary nodes compared to placebo/no treatment controls. The NATO study also demonstrated an overall survival benefit.
One prospective, double-blind, randomized study (NSABP-14) demonstrated a significant improvement in disease-free survival for NOLVADEX compared to placebo when used adjuvantly following total mastectomy and axillary dissection or segmental resection, axillary dissection, and breast radiation in women with axillary node-negative breast cancer whose tumors were estrogen receptor positive (≥ 10 fmol/mg cytosol protein). The benefit was apparent in both women under age 50 and those aged 50 years or more. 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.
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. However, the data from the randomized studies do not suggest an adverse effect. A limited number of premenopausal patients with disease progression during NOLVADEX therapy responded to subsequent ovarian ablation.

### INDICATIONS AND USAGE
**Adjuvant Therapy:** NOLVADEX is effective in delaying recurrence following total mastectomy and axillary dissection or segmental mastectomy, axillary dissection, and breast irradiation in women with axillary node-negative breast cancer. 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 is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer ($T_{1-3}$, $N_1$, $M_0$). In some NOLVADEX adjuvant studies, most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.
The estrogen and progesterone receptor values may help to predict whether adjuvant NOLVADEX therapy is likely to be beneficial.
**Therapy for Advanced Disease:** NOLVADEX is effective in the treatment of metastatic breast cancer in women. In premenopausal women with metastatic breast cancer, NOLVADEX is an alternative to oophorectomy or ovarian irradiation. Available evidence indicates that patients whose tumors are estrogen receptor positive are more likely to benefit from NOLVADEX therapy.

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

### WARNINGS
Visual disturbance including corneal changes, cataracts and retinopathy have been reported in patients receiving NOLVADEX.
As with other additive hormonal therapy (estrogens and androgens), hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with NOLVADEX. If hypercalcemia does occur, appropriate measures should be taken and, if severe, NOLVADEX should be discontinued.
A small number of cases of endometrial hyperplasia and endometrial polyps have been reported in association with NOLVADEX treatment. A definitive relationship to NOLVADEX therapy has not been established.
In a single large randomized trial in Sweden of adjuvant tamoxifen 40 mg/day for 2–5 years, an increased incidence of endometrial cancer was noted. Thirteen of 931 tamoxifen treated patients versus 2 of 915 controls developed cancer of the body of the uterus [RR = 6.4 (1.4 – 28), P < 0.01]. However, in a review of more than 12,000 patients entered into twelve other large ongoing adjuvant studies (including NSABP B-14) in which patients have received NOLVADEX 20–40 mg/day for periods of 1–5+ years versus control, no increased incidence of cancer of the uterus was seen.
In the same Swedish trial, the incidence of second primary breast tumors was reduced in the tamoxifen arm (P < 0.05). In the NSABP B-14 trial in which patients were randomized to NOLVADEX 20 mg/day for 5 years versus placebo, the incidence of second primary breast cancers is also reduced.
**Pregnancy Category D:** NOLVADEX may cause fetal harm when administered to a pregnant woman. Individuals should not become pregnant while taking NOLVADEX and should use barrier or nonhormonal contraceptive measures. Effects on reproductive functions are expected from the antiestrogenic properties of the drug. In reproductive studies in rats at dose levels equal to or below the human dose, nonteratogenic developmental skeletal changes were seen and were found to be reversible. In addition, in fertility studies in rats and in teratology studies in rabbits using doses at or below those used in humans, a lower incidence of embryo implantation and a higher incidence of fetal death or retarded in utero growth were observed, with slower learning behavior in some rat pups. The impairment of learning behavior did not achieve statistical significance in one study, and, in another study where significance was reported, this was by comparing dosed animals with controls of another study. Several pregnant marmosets were dosed during organogenesis or in the last half of pregnancy. No deformations were seen, and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. There are no adequate and well-controlled studies in pregnant women. There have been reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

### PRECAUTIONS
**General:** NOLVADEX should be used cautiously in patients with existing leukopenia or thrombocytopenia. Observations of leukopenia and thrombocytopenia occasionally have been made, but it is uncertain if these effects are due to NOLVADEX therapy. Transient decreases in platelet counts, usually to 50,000–100,000/$mm^3$, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. No hemorrhagic tendency has been recorded, and the platelet counts returned to normal levels even though treatment with NOLVADEX continued.
**Information for Patients:** Women taking NOLVADEX should be instructed to report abnormal vaginal bleeding which should be promptly investigated.
**Laboratory Tests:** Periodic complete blood counts, including platelet counts, may be appropriate.
**Drug Interactions:** When NOLVADEX is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.
**Drug/Laboratory Testing Interactions:** During postmarketing surveillance, $T_4$ 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.

NSABP B-14 STUDY

| Adverse Effect | NOLVADEX (n=1376) No. of Patients (%) | | Placebo (n=1396) No. of Patients (%) | |
|---|---|---|---|---|
| Hot flashes | 787 | (57) | 566 | (41) |
| Fluid retention | 339 | (25) | 326 | (23) |
| Vaginal discharge | 330 | (24) | 160 | (12) |
| Irregular menses | 264 | (19) | 203 | (15) |
| Nausea | 255 | (19) | 235 | (17) |
| Skin rash | 180 | (13) | 150 | (11) |
| Diarrhea | 106 | (8) | 129 | (9) |
| Vomiting | 25 | (2) | 16 | (1) |
| Phlebitis | 15 | (1) | 2 | (<1) |
| Thrombocytopenia* | 10 | (1) | 4 | (<1) |
| Leukopenia** | 7 | (1) | 10 | (1) |

*Defined as a platelet count of $<100{,}000/mm^3$
**Defined as a white blood cell count of $<3000/mm^3$

Endocrine changes in immature and mature mice were investigated in a 13-month study. Granulosa cell ovarian tumors and interstitial cell testicular tumors were found in mice receiving NOLVADEX, but not in the controls.

**Mutagenesis:** No genotoxic potential has been found in a battery of in vivo and in vitro tests with pro- and eukaryotic test systems with drug metabolizing systems present.

**Impairment of Fertility:** Fertility in female rats was decreased following administration of 0.04 mg/kg for two weeks prior to mating through day 7 of pregnancy. There was a decreased number of implantations, and all fetuses were found dead.

Following administration to rats of 0.16 mg/kg from days 7–17 of pregnancy, there were increased numbers of fetal deaths. Administration of 0.125 mg/kg to rabbits during days 6–18 of pregnancy resulted in abortion or premature delivery. Fetal deaths occurred at higher doses. There were no teratogenic changes in either rat or rabbit segment II studies. Several pregnant marmosets were dosed with 10 mg/kg/day either during organogenesis or in the last half of pregnancy. No deformations were seen, and although the dose was high enough to terminate pregnancy in some animals, those that did maintain pregnancy showed no evidence of teratogenic malformations. Rats given 0.16 mg/kg from day 17 of pregnancy to 1 day before weaning demonstrated increased numbers of dead pups at parturition. It was reported that some rat pups showed slower learning behavior, but this did not achieve statistical significance in one study, and in another study where significance was reported, this was obtained by comparing dosed animals with controls of another study.

The recommended daily human dose of 20–40 mg corresponds to 0.4–0.8 mg/kg for an average 50 kg woman.

**Pregnancy Category D:** See WARNINGS.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NOLVADEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

## ADVERSE REACTIONS

Adverse reactions to NOLVADEX are relatively mild and rarely severe enough to require discontinuation of treatment. If adverse reactions are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease.

In patients treated with NOLVADEX for metastatic breast cancer, the most frequent adverse reactions to NOLVADEX are hot flashes and nausea and/or vomiting. These may occur in up to one-fourth of patients.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities and skin rash. Usually these have not been of sufficient severity to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and, also, local disease flare have occurred, which are sometimes associated with a good tumor response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of preexisting lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting NOLVADEX and generally subside rapidly.

Other adverse reactions which are seen infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, light-headedness and headache.

There have been infrequent reports of thromboembolic events occurring during NOLVADEX therapy. Since for cancer patients in general an increased incidence of thromboembolic events is known to occur, a causal relationship to NOLVADEX remains conjectural. An increased incidence has been reported when cytotoxic agents are combined with NOLVADEX.

Ovarian cysts have been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with NOLVADEX.

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

In the ongoing NSABP study B-14, patients with axillary node-negative breast cancer were randomized to 5 years of NOLVADEX or placebo following primary surgery. The reported adverse effects are tabulated below (mean follow-up of 29 months). The incidence of hot flashes (57% v 41%), vaginal discharge (24% v 12%), and irregular menses (19% v 15%) were higher with NOLVADEX compared with placebo. The incidence of all other adverse effects were similar in the two treatment groups with the exception of thromboembolic events (phlebitis), which although rare, were more common with NOLVADEX than with placebo. [See table above.]

In the Eastern Cooperative Oncology Group (ECOG) adjuvant breast cancer trial, NOLVADEX or placebo was administered for 2 years to patients following mastectomy. When compared to placebo, NOLVADEX showed a significantly higher incidence of hot flashes (19% versus 8% for placebo). The incidence of all other adverse reactions was similar in the 2 treatment 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), patients received either NOLVADEX or no therapy. In the Toronto study, hot flashes and nausea and/or vomiting were observed in 29% and 19% of patients, respectively, for NOLVADEX versus 1% and 0% in the untreated group. In the NATO trial, hot flashes, nausea and/or vomiting and vaginal bleeding were reported in 2.8%, 2.1%, and 2.0% of patients, respectively, for NOLVADEX versus 0.2% for each in the untreated group.

The following table summarizes the incidence of adverse reactions reported at a frequency of 2% or greater from clinical trials (Ingle, Pritchard, Buchanan) which compared NOLVADEX therapy to ovarian ablation in premenopausal patients with metastatic breast cancer.

[See table below.]

| Adverse Reactions* | NOLVADEX All Effects Number of Patients (%) n=104 | | OVARIAN ABLATION All Effects Number of Patients (%) n=100 | |
|---|---|---|---|---|
| Flush | 34 | (32.7) | 46 | (46) |
| Amenorrhea | 17 | (16.3) | 69 | (69) |
| Altered Menses | 13 | (12.5) | 5 | (5) |
| Oligomenorrhea | 9 | (8.7) | 1 | (1) |
| Bone Pain | 6 | (5.7) | 6 | (6) |
| Menstrual Disorder | 6 | (5.7) | 4 | (4) |
| Nausea | 5 | (4.8) | 4 | (4) |
| Cough/Coughing | 4 | (3.8) | 1 | (1) |
| Edema | 4 | (3.8) | 1 | (1) |
| Fatigue | 4 | (3.8) | 1 | (1) |
| Musculoskeletal Pain | 3 | (2.8) | 0 | (0) |
| Pain | 3 | (2.8) | 4 | (4) |
| Ovarian Cyst(s) | 3 | (2.8) | 2 | (2) |
| Depression | 2 | (1.9) | 2 | (2) |
| Abdominal Cramps | 1 | (1) | 2 | (2) |
| Anorexia | 1 | (1) | 2 | (2) |

*Some patients had more than one adverse reaction.

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

One or two 10 mg tablets twice a day (morning and evening). In three single agent adjuvant studies, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years (see *Clinical Pharmacology*). In the ongoing NSABP study B-14, one 10 mg NOLVADEX tablet is being given twice a day for five years. The optimal duration of adjuvant therapy is not known.

## HOW SUPPLIED

Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. Protect from heat and light. NDC 0310-0600.

Rev Z 05/90

ICI Pharma
A business unit of ICI Americas Inc.
Wilmington, DE 19897 USA

*Shown in Product Identification Section, page 412*

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**SORBITRATE®** ℞
[*sorb'i-trate*]
**(Isosorbide Dinitrate)**

## DESCRIPTION

SORBITRATE® (isosorbide dinitrate), an organic nitrate, is a vasodilator with effects on both arteries and veins. SORBITRATE is available as:

**SORBITRATE® SUBLINGUAL**

**2.5 mg Sublingual Tablet.** Each tablet contains 2.5 mg of isosorbide dinitrate.
Inactive ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.

**5 mg Sublingual Tablet.** Each tablet contains 5 mg of isosorbide dinitrate.
Inactive ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Red 7.

**10 mg Sublingual Tablet.** Each tablet contains 10 mg of isosorbide dinitrate.
Inactive ingredients: corn starch, lactose (hydrous), magnesium stearate, Yellow 10.

**SORBITRATE® CHEWABLE**

**5 mg Chewable Tablet.** Each tablet contains 5 mg of isosorbide dinitrate.
Inactive ingredients: Blue 1, confectioner's sugar, corn starch, flavor, hydrogenated vegetable oil, magnesium stearate, mannitol, povidone, Yellow 10.

**10 mg Chewable Tablet.** Each tablet contains 10 mg of isosorbide dinitrate.
Inactive ingredients: confectioner's sugar, corn starch, flavor, hydrogenated vegetable oil, magnesium stearate, mannitol, povidone, Yellow 10.

**SORBITRATE® ORAL**

**5 mg Oral Tablet.** Each tablet contains 5 mg of isosorbide dinitrate.
Inactive ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.

***Continued on next page***