soltamox®

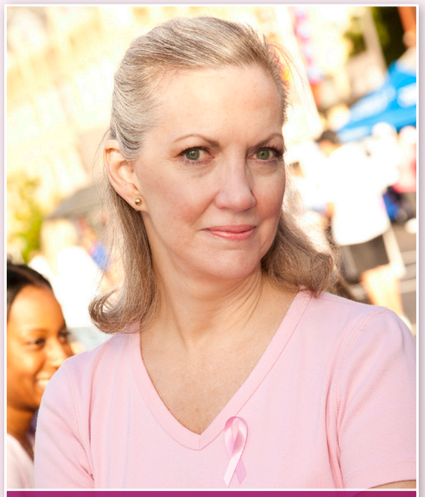
(tamoxifen citrate) oral solution

Offering Tamoxifen Patients a Therapeutic OPTION

Soltamox (tamoxifen citrate) oral solution is indicated for the treatment of metastatic breast cancer in women and men; for the adjuvant treatment of node-positive breast cancer in postmenopausal women and for the adjuvant treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation; for the reduction in risk of invasive breast cancer in women with ductal carcinoma *in situ*, following breast surgery and radiation; and to reduce the incidence of breast cancer in women at high risk for breast cancer.

Patients may benefit from Soltamox if they find it easier to take liquid medications or if they have difficulty swallowing tablets. Soltamox is now available with Zero Copay for qualified patients.[a]

Joan S, Age 43
Diagnosed as being at high risk for breast cancer
Likes being offered a choice – finds it easier to take liquid medications



Caroline P, Age 50
Newly diagnosed with invasive breast cancer
On multiple medications – attracted to Zero Copay

Jennifer S, Age 55
Diagnosed 3 years ago with metastatic breast cancer – has difficulty swallowing tablets

Patients are representative only and are not photos of actual patients.

[a]**Terms and Conditions:** Certain patients in federal programs may not qualify. Qualified patients will pay $0 per Soltamox prescription. After a maximum reimbursement allowance of $100 for Soltamox[b] any remaining costs will be the responsibility of the patient. Copay assistance is not valid for prescriptions reimbursed in whole or in part under Medicaid, Medicare, including Medicare Advantage and Part D prescription drug plans, or any other federal or state program (including state pharmaceutical assistance programs) or where prohibited, taxed, or otherwise restricted. DARA BioSciences reserves the right to rescind, revoke, or amend this offer without notice. Patients understand and agree to comply with the terms and conditions of this offer as set forth here.
[b]Based on a one month prescription of 300 mL. Lesser dosages will have a reduced maximum benefit.

IMPORTANT SAFETY INFORMATION

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. 0.0 for placebo).* For stroke, the incidence rate per 1,000 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.

*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** in Prescribing Information.

See Table 3 under **CLINICAL PHARMACOLOGY, Clinical Studies in Prescribing Information.

Please see ISI on back and full Prescribing Information accompanying this brochure.

soltamox®

(tamoxifen citrate) oral solution

Offering Tamoxifen Patients a Therapeutic **OPTION**

Tamoxifen citrate - Proven Efficacy[1]

- In women with ER-positive or ER-unknown breast cancer receiving tamoxifen as adjuvant therapy, the reduction in breast cancer recurrence at around 5 years was 47%, with a concomitant 26% reduction in mortality
- In women with ductal carcinoma *in situ*, tamoxifen reduced the incidence of invasive breast cancer by 43% vs. placebo (P=0.004)
- In women at high risk for breast cancer,[c] tamoxifen reduced the incidence of invasive breast cancer by 44% vs. placebo (P<0.00001), after a median follow-up of 4.2 years

[c]High risk is defined as women at least 35 years of age with a 5-year predicted risk of breast cancer ≥1.67%, as calculated by the Gail Model.

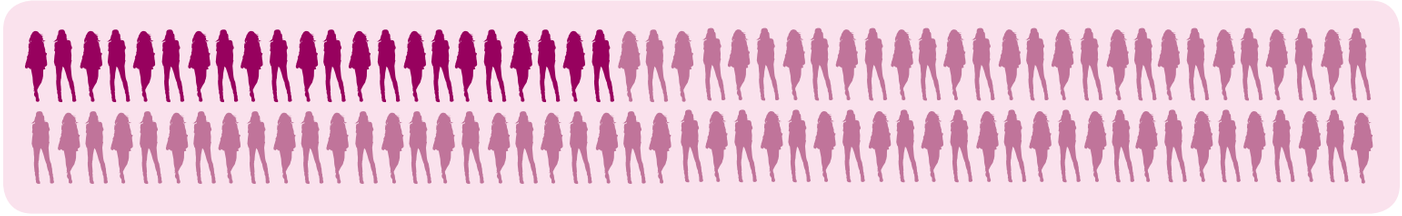
Tamoxifen citrate - An Established Side Effect and Safety Profile[1]

- Over 35 years' experience in the US (first approved in 1977 for metastatic breast cancer)
- Tamoxifen citrate is contraindicated in women who require concomitant coumadin-type anticoagulant therapy, in women with a history of deep vein thrombosis or pulmonary embolus, and in women with known hypersensitivity to the drug or any of its ingredients.
- The most common adverse reactions (≥20% incidence) associated with tamoxifen are hot flashes, fluid retention, vaginal discharge, vaginal bleeding, vasodilatation, nausea, irregular menses, weight loss, and musculoskeletal events.

Interest in Soltamox (tamoxifen citrate) Oral Solution Expressed Among Breast Cancer Patients[2]

- Results of CAPTURE (Compliance and Preference for Tamoxifen Registry),[2] an IRB-approved survey of 626 female breast cancer patients taking tamoxifen tablets, indicated that over 20% of patients were willing to try an oral liquid form of tamoxifen when presented with a choice

22% of women indicated a willingness to try a liquid formulation of tamoxifen



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(tamoxifen citrate) oral solution

Offering Tamoxifen Patients a Therapeutic **OPTION**

Soltamox® (tamoxifen citrate) oral solution

Qualified patients
Pay $0 Copay
for each Soltamox® prescription[a]

- Bioequivalent to tamoxifen tablets
- Exact same indications, side effects, and safety profile as tamoxifen tablets
- Colorless, sugar-free liquid
- Licorice flavor
- 20 mg dose of Soltamox is administered as 10 mL (equivalent to 2 teaspoons) of the oral solution
- Zero copay for qualified patients[a]

[a]Terms and Conditions: Certain patients in federal programs may not qualify. Qualified patients will pay $0 per Soltamox prescription. After a maximum reimbursement allowance of $100 for Soltamox[b] any remaining costs will be the responsibility of the patient. Copay assistance is not valid for prescriptions reimbursed in whole or in part under Medicaid, Medicare, including Medicare Advantage and Part D prescription drug plans, or any other federal or state program (including state pharmaceutical assistance programs) or where prohibited, taxed, or otherwise restricted. DARA BioSciences reserves the right to rescind, revoke or amend this offer without notice. Patients understand and agree to comply with the terms and conditions of this offer as set forth here.

[b]Based on a one month prescription of 300 mL. Lesser dosages will have a reduced maximum benefit.

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 tamoxifen. If hypercalcemia does occur, appropriate measures should be taken and, if severe, tamoxifen should be discontinued.

Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma

An increased incidence of uterine malignancies has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen. Most uterine malignancies seen in association with tamoxifen are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors, have also been reported. Uterine sarcoma is generally associated with a higher FIGO stage (III/IV) at diagnosis, poorer prognosis, and shorter survival. Uterine sarcoma has been reported to occur more frequently among long term users (≥2 years) of tamoxifen than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal.

Any patient receiving or who has previously received tamoxifen who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received tamoxifen should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, eg, menstrual irregularities, abnormal vaginal bleeding, change in vaginal discharge, or pelvic pain or pressure.

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IMPORTANT SAFETY INFORMATION

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. 0.0 for placebo).* For stroke, the incidence rate per 1,000 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.

*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 in Prescribing Information.

**See Table 3 under CLINICAL PHARMACOLOGY, Clinical Studies in Prescribing Information.

Tamoxifen citrate is contraindicated in women who require concomitant coumadin-type anticoagulant therapy, in women with a history of deep vein thrombosis or pulmonary embolus, and in women with known hypersensitivity to the drug or any of its ingredients.

Hypercalcemia in Metastatic Breast Cancer Patients
Hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen. If hypercalcemia does occur, appropriate measures should be taken and, if severe, tamoxifen should be discontinued.

Endometrial Cancer and Uterine Sarcoma
An increased incidence of uterine malignancies has been reported in association with tamoxifen treatment; most are classified as adenocarcinoma of the endometrium. Rare uterine sarcomas, including malignant mixed mullerian tumors, have also been reported. Uterine sarcoma has been reported to occur more frequently among long-term users (≥2 years) of tamoxifen than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal. Any patient receiving or who has previously received tamoxifen should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, eg, menstrual irregularities, abnormal vaginal bleeding, change in vaginal discharge, or pelvic pain or pressure.

Non-Malignant Effects on the Uterus
An increased incidence of endometrial changes including hyperplasia and polyps has been reported in association with tamoxifen treatment. Reports of endometriosis, uterine fibroids, ovarian cysts, menstrual irregularity, and amenorrhea have been reported in women receiving tamoxifen.

Thromboembolic Effects
There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen therapy. When tamoxifen is coadministered 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. There was a non-statistically-significant increase in stroke among patients randomized to tamoxifen in a study (NSABP P-1) of the reduction in breast cancer incidence in high risk women (24 – placebo; 34 – tamoxifen; RR=1.42; 95% CI 0.82 – 2.51). Among these strokes, 3 strokes in the placebo group and 4 strokes in the tamoxifen group were fatal.

Liver Cancer
Three cases of liver cancer were reported in the tamoxifen group vs. 1 case in the observation group in a trial using adjuvant tamoxifen 40 mg/day for 2-5 years. One case of liver cancer was reported in another trial in a participant receiving tamoxifen. No other cases of liver cancer have been reported to date in other clinical trials evaluating tamoxifen.

Non-Malignant Effects on the Liver
Tamoxifen has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more serious liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases were fatal. In most reported cases, the relationship to tamoxifen is uncertain, although some positive rechallenges and dechallenges have been reported.

Other Cancers
A number of secondary primary tumors, occurring at sites other than the endometrium, have been reported following the treatment of breast cancer with tamoxifen in clinical trials, although the 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 disturbance, 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.

Pregnancy Category D
Tamoxifen may cause fetal harm when administered to a pregnant woman. Women 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. For sexually active women of child-bearing potential, tamoxifen therapy should be initiated during menstruation, or immediately following a negative ß-HCG test. 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, 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.

Precautions
Decreases in platelet counts, usually to 50,000 – 100,000/mm^3, 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 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 tamoxifen; this can sometimes be severe.

Nursing Mothers
Tamoxifen has been reported to inhibit lactation. It is not known if tamoxifen is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from tamoxifen, women taking tamoxifen should not breast feed.

Laboratory Tests and Monitoring
Periodic complete blood counts, including platelet counts, and periodic liver function tests should be obtained. Periodic monitoring of plasma triglycerides and cholesterol may be indicated in patients with pre-existing hyperlipidemias. Women taking or having previously taken tamoxifen should 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 have a breast examination, a mammogram, and a gynecologic examination prior to initiating and while on tamoxifen therapy.

Drug Interactions
Use caution when coadministering coumadin-type anticoagulants, as a significant increase in anticoagulant effect may occur. Careful monitoring of patient's prothrombin time is recommended. 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%, however the effect of tamoxifen on metabolism and excretion of other antineoplastic drugs is not known. Tamoxifen should not be administered with anastrozole.

Adverse Reactions
The most common adverse reactions (incidence ≥20%) were hot flashes, fluid retention, vaginal discharge, vaginal bleeding, vasodilatation, nausea, irregular menses, weight loss, and musculoskeletal events.

Laboratory Abnormalities
During postmarketing surveillance, T4 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 karyopyknotic index on vaginal smears and various degrees of estrogen effect on Pap smears have been infrequently reported in post-menopausal women given tamoxifen. Infrequent cases of hyperlipidemias have been reported.

INDICATIONS AND DOSAGE

Metastatic Breast Cancer
Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, tamoxifen citrate 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 tamoxifen citrate therapy.

Adjuvant Treatment of Breast Cancer
Tamoxifen citrate 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 tamoxifen citrate adjuvant studies, most of the benefit to date has been in the subgroup with four or more positive axillary nodes.

Tamoxifen citrate is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. The estrogen and progesterone receptor values may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial. Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant tamoxifen citrate therapy for breast cancer.

Ductal Carcinoma in Situ (DCIS)
In women with DCIS, following breast surgery and radiation, tamoxifen citrate is indicated to reduce the risk of invasive breast cancer (see BOXED WARNING at the beginning of the Prescribing Information). The decision regarding therapy with tamoxifen for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen therapy. Current data from clinical trials support five years of adjuvant tamoxifen citrate therapy for patients with breast cancer.

Reduction in Breast Cancer Incidence in High Risk Women
Tamoxifen citrate 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 (see BOXED WARNING at the beginning of the Prescribing Information). Tamoxifen citrate 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 ≥1.67%, as calculated by the Gail Model. Health Care Professionals can obtain a Gail Model Risk Assessment tool by dialing 1-800-833-3533. There are no data available regarding the effect of tamoxifen citrate 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 tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of tamoxifen citrate therapy. In the NSABP P-1 trial, tamoxifen citrate treatment lowered the risk of developing breast cancer during the follow-up period of the trial, but did not eliminate breast cancer risk (see CLINICAL PHARMACOLOGY section of Prescribing Information).

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). A 20 mg dose of Soltamox® is administered as 10 mL (equivalent to 2 teaspoons) of the oral solution. In the EBCTCG 1995 overview, 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 therapy for patients with breast cancer.

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

Reduction in Breast Cancer Incidence in High Risk Women
The recommended dose is tamoxifen citrate 20 mg daily for 5 years. There are no data to support the use of tamoxifen citrate other than for 5 years.

Please see attached full Prescribing Information and complete Black Box Warning.

References:

1. Soltamox [package insert]. DARA BioSciences, Inc; 8/2012.
2. Glück S, Sharma J, Belafsky PC, et al. CAPTURE (Compliance and Preference for Tamoxifen Registry) Patient Survey Reveals Potential Strategies to Improve Long-Term Adherence to TAM Based on Choice: Results of a Large Internet-Based Survey. *J Natl Compr Canc Netw.* 2014;12(4):455-456.

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