AstraZeneca

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Dear Doctor:

AstraZeneca Pharmaceuticals LP (AstraZeneca) would like to call your attention to recent changes in the enclosed prescribing information for NOLVADEX® (tamoxifen citrate) tablets. These changes have particular relevance for women with DCIS and women at high risk for developing breast cancer who are receiving NOLVADEX or considering NOLVADEX therapy to reduce their risk of developing invasive breast cancer. While it has been known that NOLVADEX treatment is associated with an increased risk of endometrial cancer, recent information indicates that there is also an increased risk of developing a rare and more aggressive uterine sarcoma. These data, and the previously reported increased risk of stroke and pulmonary embolism, have prompted changes to the NOLVADEX label.

This important safety information has been placed at the beginning of the NOLVADEX label in order to bring to your attention information on the use of NOLVADEX for women with DCIS and women at high risk of developing breast cancer:

WARNING – For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer: Serious and life-threatening events associated with NOLVADEX 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 PHARMACOLOG –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 NOLVADEX vs. 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women-years of 0.17 for NOLVADEX vs. 0.0 for placebo*). For stroke, the incidence rate per 1,000 women-years was 1.43 for NOLVADEX vs. 1.00 for placebo. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for NOLVADEX vs. 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 NOLVADEX 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.**
****See Table 3 under CLINICAL PHARMACOLOGY-Clinical Studies.**

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WARNINGS – Effects on the Uterus – Endometrial Cancer and Uterine Sarcoma:

This section has been expanded to include additional information on the increased risk of uterine sarcomas as well as the previously noted increased risk of endometrial cancer:

An increased incidence of uterine malignancies has been reported in association with NOLVADEX treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of NOLVADEX. Most uterine malignancies seen in association with NOLVADEX 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 NOLVADEX than non-users. Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal. In an updated review of long-term data (median length of follow-up is 6.9 years), including blinded follow-up) on 8,306 women with an intact uterus at randomization in the NSABP P-1 risk reduction trial, the incidence of both adenocarcinoma and rare uterine sarcomas was increased in women taking NOLVADEX. Endometrial adenocarcinoma was reported in 53 women randomized to NOLVADEX (52 cases of FIGO Stage I and 1 Stage III endometrial adenocarcinoma) and 17 women randomized to placebo (16 cases of FIGO Stage I and 1 case of FIGO Stage II endometrial adenocarcinoma) (incidence per 1,000 women-years of 2.20 and 0.71, respectively). Some patients received post-operative radiation therapy in addition to surgery. Uterine sarcomas were reported in 4 women randomized to NOLVADEX (2 FIGO I, 1 FIGO II, 1 FIGO III. The FIGO I cases were a sarcoma and a MMMT. The FIGO II was a MMMT and the FIGO III was a sarcoma) and 0 patients randomized to placebo (Incidence per 1,000 women-years 0.17 and 0.00, respectively.) A similar increased incidence in endometrial adenocarcinoma and uterine sarcoma was observed among women receiving NOLVADEX in five other NSABP clinical trials. Any patient receiving or who has previously received NOLVADEX who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received NOLVADEX 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, changes in vaginal discharge, or pelvic pain or pressure.

These risks apply to patients receiving NOLVADEX for any indication. However, the benefits of NOLVADEX therapy in patients treated in the adjuvant setting (improved disease-free and overall survival) or for advanced disease (response and palliation), outweigh the risks. Any time NOLVADEX therapy is considered, the overall risks and benefits of this therapy should be discussed in detail with the patient.

Please take the time to read the enclosed label carefully. This information is provided to help you in your decision to prescribe NOLVADEX and also to advise patients on the relative risks and benefits of such therapy. AstraZeneca believes that the proven efficacy of NOLVADEX outweighs the risks for women with breast cancer. In addition,

AstraZeneca believes that there are clear benefits of NOLVADEX therapy for many women with DCIS or who are at high risk of developing breast cancer, but that the risks of NOLVADEX therapy should be individually considered before commencement of therapy.

AstraZeneca will continue to monitor the safety of NOLVADEX. Whenever important new data become available, the label will be modified accordingly, and you will be notified.

Sincerely yours,

Joseph D Purvis, M.D.

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Enclosure

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