PRODUCT MONOGRAPH

Pr TEVA-TAMOXIFEN

(tamoxifen citrate)

10 and 20 mg Tablets, BP

Antineoplastic Agent

Teva Canada Limited
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Toronto, ON
M1B 2K9
Canada
www.tevacanada.com

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August 31, 2015

Control #: 185417
Tamoxifen citrate therapy was associated with serious and life-threatening events including uterine malignancies, stroke, pulmonary embolism, and deep vein thrombosis in the NSABP P-1 trial for the prevention of breast cancer. The use of TEVA-TAMOXIFEN for breast cancer prevention is not an approved indication in Canada. In the NSABP P-1 trial, the relative risk of tamoxifen citrate compared to placebo was 3.1 for endometrial cancer, 4.0 for uterine sarcomas, 1.6 for stroke, 3.0 for pulmonary embolism, and 1.6 for deep vein thrombosis. These events were fatal in some patients. Health care providers should be aware of the possible risks associated with TEVA-TAMOXIFEN therapy and should discuss them with their patients.

THE BENEFITS OF TAMOXIFEN CITRATE THERAPY OUTWEIGH THE RISKS IN THE MAJORITY OF WOMEN BEING TREATED ACCORDING TO THE APPROVED CANADIAN INDICATION FOR THE TREATMENT OF BREAST CANCER.

ACTIONS AND CLINICAL PHARMACOLOGY

Tamoxifen citrate, the active ingredient, is a non-steroidal agent which has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects are related to its ability to compete with estrogen for binding sites in target tissues such as breast and uterus. Tamoxifen citrate inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In the rat model, tamoxifen citrate appears to exert its antitumor effects by binding to estrogen receptors.

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

In women with estrogen receptor-positive/unknown breast tumours, adjuvant tamoxifen citrate has been shown to significantly reduce recurrence of the disease and improve 10-year survival, achieving a significantly greater effect with five years treatment than with one or two years treatment. These benefits appear to be largely irrespective of age, menopausal status, tamoxifen citrate dose and additional chemotherapy.
Ranges as large as 0 to 300 fmol/mg protein have been reported in histologically comparable portions of the same tumor. In addition, the collection, transport and storage of tumor specimens can affect the validity of current estrogen receptor assays.

The apparent discrepancy in correlation between estrogen receptor status and clinical response may also be explained by recent in vitro evidence indicating that not all of the growth inhibiting effects of tamoxifen citrate are mediated through the estrogen receptor. Tamoxifen citrate has been shown to have a low affinity for the androgen receptor and on a binding site distinct from the estrogen receptor. The possibility also exists that tamoxifen citrate interferes with the action of hormonal steroids on cell growth, that it could modulate the action of peptide hormones at their receptors by effects on cell membranes, and that it inhibits prostaglandin synthetase thereby having the potential to limit tumour growth. It is recognized that tamoxifen citrate also displays estrogenic-like effects on several body systems including the endometrium, bone and blood lipids.

**Bioavailability:**

A comparative two-way, single-dose bioavailability study was performed on TEVA-TAMOXIFEN (tamoxifen citrate) 20 mg film-coated tablets and NOLVADEX®-D 20 mg film-coated tablets. Ten normal male volunteers completed the randomized two-way, crossover study. A washout period of 8 weeks separated each study phase. Blood samples for analysis were taken directly before administration and at specified times thereafter for a period of 21 days. Plasma levels of tamoxifen were measured by a validated HPLC assay method. The pharmacokinetic data (mean ± standard deviation) calculated for the TEVA-TAMOXIFEN and NOLVADEX®-D film-coated tablet formulations, is tabulated below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Indices for Tamoxifen</th>
<th>TEVA-TAMOXIFEN (1 x 20 mg)</th>
<th>NOLVADEX®-D (1 x 20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area Under the Curve: AUC (ngXhr/mL); 0-4</td>
<td>2334.48 ± 852.0</td>
<td>2466.96 ± 758.4</td>
</tr>
<tr>
<td>Area Under the Curve: AUC (ngXhr/mL); 0-21 days</td>
<td>2141.52 ± 759.6</td>
<td>2243.28 ± 621.6</td>
</tr>
<tr>
<td>Peak Plasma Concentration: C_max (ng/mL)</td>
<td>32.67 ± 10.34</td>
<td>32.99 ± 6.61</td>
</tr>
<tr>
<td>Time of Peak Plasma Level: T_max (hours)</td>
<td>5.52 ± 0.48</td>
<td>5.28 ± 0.72</td>
</tr>
</tbody>
</table>

Statistical evaluation by analysis of variance (ANOVA) of AUC 0-∞, AUC 0-21 days, C_max and T_max showed no significant difference between the two formulations. Details of this comparative bioavailability study are available from Teva Canada Limited upon request.

In another study, a two-group parallel single-dose bioavailability study was performed on TEVA-TAMOXIFEN 20 mg uncoated tablets and NOLVADEX®-D 20 mg film-coated
tablets. A total of sixty-nine normal male volunteers were randomly divided into two groups and they all completed the randomized two-group, parallel study. Blood samples for analysis were taken directly before administration and at specified times thereafter for a period of 24 days. Plasma levels of tamoxifen were measured by a validated HPLC assay method. The pharmacokinetic data calculated for the TEVA-TAMOXIFEN uncoated and NOLVADEX®-D film-coated tablet formulations is tabulated below:

### Pharmacokinetic Indices for Tamoxifen

<table>
<thead>
<tr>
<th></th>
<th>TEVA-TAMOXIFEN (1 x 20 mg)</th>
<th>NOLVADEX®-D** (1 x 20 mg)</th>
<th>Ratio of Geometric Means (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt; (ngXhr/mL)</td>
<td>1922.9 (28)</td>
<td>2086.5 (33)</td>
<td>92</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (ngXhr/mL)</td>
<td>763.4 (22)</td>
<td>819.7 (27)</td>
<td>93</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;4&lt;/sub&gt; (ngXhr/mL)</td>
<td>2154.1 (30)</td>
<td>2327.4 (34)</td>
<td>93</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>27.31 (26)</td>
<td>29.48 (27)</td>
<td>93</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; *(hr)</td>
<td>5.2 (34)</td>
<td>5.0 (26)</td>
<td>--</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;* *(hr)</td>
<td>180.0 (27)</td>
<td>177.3 (30)</td>
<td>--</td>
</tr>
</tbody>
</table>

* For the T<sub>max</sub> and T<sub>1/2</sub> parameters these are the arithmetic means (standard deviation).

**NOLVADEX®-D is manufactured by Zeneca Pharma Inc. (Canada), Mississauga, Ontario

### INDICATIONS

TEVA-TAMOXIFEN (tamoxifen citrate) is indicated for the adjuvant treatment of early breast cancer in women with estrogen receptor positive tumors.

TEVA-TAMOXIFEN is indicated for the treatment of women with hormone responsive locally advanced / metastatic breast cancer.

### CONTRAINDICATIONS

TEVA-TAMOXIFEN (tamoxifen citrate) is contraindicated in patients with hypersensitivity to the product or any of its components.

Tamoxifen must not be given during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and fetal deaths after women have taken tamoxifen, although no causal relationship has been established.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

In rodent models of fetal reproductive tract development, tamoxifen was associated with changes similar to those caused by estradiol, ethynylestradiol, clomiphene and diethylstilboestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who
were exposed to DES in utero and who have a 1 in 1000 risk of developing clear-cell carcinoma of the vagina or cervix. Only a small number of pregnant women have been exposed to tamoxifen citrate. Such exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed in utero to tamoxifen citrate.

Women should be advised not to become pregnant while taking tamoxifen citrate and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal patients must be carefully examined before treatment to exclude the possibility of pregnancy. Women should be informed of the potential risks to the fetus, should they become pregnant while taking tamoxifen citrate or within two months of cessation of therapy.

When used in the prevention setting (an indication not approved in Canada), tamoxifen citrate is contraindicated in patients with a history of stroke, deep venous thrombosis or pulmonary embolism, and in patients who are at an increased risk of developing endometrial cancer.

WARNINGS

TEVA-TAMOXIFEN (tamoxifen citrate) should be used only for the conditions listed under the INDICATIONS section.

An increased incidence of uterine malignancies has been reported in association with tamoxifen citrate treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen citrate. Most uterine malignancies seen in association with tamoxifen citrate are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed Mullerian tumours, 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 citrate than non-users.

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, occurring commonly during tamoxifen citrate therapy (see ADVERSE REACTIONS). When tamoxifen citrate is co-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 citrate should be carefully considered in women with a history of thromboembolic events.

An increased risk of stroke has been found to be associated with tamoxifen citrate therapy in high-risk patients being treated for the prevention of breast cancer. The use of tamoxifen citrate for the prevention of breast cancer is not an approved indication in Canada.
Incidence rates for the following events were estimated from a long-term clinical study called the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention (NSABP P-1) Trial. In this trial, high-risk patients were randomized to either tamoxifen therapy or placebo, for the prevention of breast cancer. Uterine malignancies were separated into cases of endometrial adenocarcinomas and uterine sarcomas. The relative risk of tamoxifen citrate compared to placebo was 3.1 for endometrial cancer, 4.0 for uterine sarcomas, 1.6 for stroke, 3.0 for pulmonary embolism, and 1.6 for deep vein thrombosis.

Disturbances of menstrual function, including oligomenorrhea and amenorrhea, have been reported in a proportion of pre-menopausal women receiving tamoxifen citrate for the treatment of breast cancer. Available information indicates that in those women receiving tamoxifen citrate for up to two years for the treatment of early breast cancer who develop disturbances of menstrual function on treatment, a proportion return to normal cyclical bleeding on cessation of therapy.

Hepatocellular carcinomas have been reported in a 2 year oncogenicity study in rats receiving tamoxifen citrate (see TOXICOLOGY). In addition, gonadal tumors have been reported in mice receiving tamoxifen citrate in long-term studies (see TOXICOLOGY). The clinical relevance of these cancer findings has not been established.

Cataracts were also reported in the 2 year oncogenicity study in rats, and since then it has been established that treatment with tamoxifen citrate has been associated with an increased incidence of cataracts.

The use of some hormonal agents in breast cancer therapy has been associated with myalgia. Myalgia has been reported in patients receiving tamoxifen citrate in clinical trials and the postmarket setting (see ADVERSE REACTIONS). In clinical trials, the incidence of myalgia was similar between patients treated with tamoxifen or an aromatase inhibitor reported to be associated with this event. In post-market reports, discontinuation of treatment resulted in resolution of symptoms.

A number of second primary tumors, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following the treatment of breast cancer patients with tamoxifen. No causal link has been established and the clinical significance of these observations remains unclear.

As tamoxifen citrate has been associated with increased rates of thromboembolic events, tamoxifen citrate may increase the risk of complications after microvascular breast reconstruction. A retrospective study found that women taking tamoxifen citrate within 28 days of undergoing delayed breast reconstruction had a higher rate of complications (21.5%), including total flap loss (3.9%), compared to women who had not received tamoxifen citrate within 28 days of surgery (15% and 0.4%, respectively). Of the total flap losses, 90% were due to either venous or arterial thrombosis. Consideration should be given to temporarily interrupt tamoxifen citrate before undergoing delayed microvascular breast reconstruction after a careful individual benefit/risk assessment.
Tamoxifen citrate is a pro-drug requiring metabolic activation by CYP2D6. Low CYP2D6 activity that occurs in patients harbouring certain CYP2D6 alleles (i.e. *4) or from the chronic use of CYP2D6 inhibitors can lead to persistent reductions in plasma concentrations of an active metabolite of tamoxifen citrate (endoxifen). Reduced efficacy on tamoxifen citrate has been reported with concomitant usage of some selective serotonin reuptake inhibitor (SSRI) antidepressants (e.g. paroxetine, a known CYP2D6 inhibitor). Concurrent chronic use of CYP2D6 inhibitors that may affect tamoxifen citrate efficacy should be avoided if possible (see also PRECAUTIONS, Drug Interactions).

PRECAUTIONS
TEVA-TAMOXIFEN (tamoxifen citrate) should be used cautiously in patients with existing thrombocytopenia or leucopenia. Decreases in platelet counts, usually to 80,000-90,000/mm³, infrequently lower, have been observed occasionally during treatment with tamoxifen citrate. However, no hemorrhagic tendency has been reported and the platelet counts returned to normal levels even though treatment with tamoxifen citrate was continued.

Transient decreases in leukocytes also have been observed occasionally during treatment. Although it was uncertain if these occasional incidences of leukopenia and thrombocytopenia were due to tamoxifen citrate therapy, complete blood counts, including platelet counts, should be obtained periodically.

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 citrate. Any symptoms suggestive of hypercalcemia should be evaluated promptly. Patients who have metastatic bone disease should have periodic serum calcium determinations during the first few weeks of TEVA-TAMOXIFEN therapy. If hypercalcemia is present, appropriate measures should be taken and, if severe, TEVA-TAMOXIFEN should be discontinued.

The first patient follow-up should be done within one month following initiation of treatment. Thereafter, examinations may be performed at one to two month intervals.

Bone pain, if it should occur, may require the use of analgesics.

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen citrate treatment. The incidence and pattern of this increase suggest that the underlying mechanism may be related to estroggenic properties of tamoxifen citrate. Any patients receiving tamoxifen citrate or having previously received tamoxifen who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated.

In clinical studies, the median duration of treatment before the onset of a definite objective response has been two months. However, approximately one-quarter of
patients who eventually responded were treated for four or more months before a definite objective response was recorded.

The duration of treatment with TEVA-TAMOXIFEN will depend on the patient's response. The drug should be continued as long as there is a favourable response (See DOSAGE AND ADMINISTRATION).

With obvious disease progression, the drug should be discontinued. However, because an occasional patient will have a local disease flare (see description under ADVERSE REACTIONS) or an increase in bone pain shortly after starting tamoxifen citrate, it is sometimes difficult during the first few weeks of treatment to determine whether the patient's disease is progressing or whether it will stabilize or respond to continued treatment. There are data to suggest that, if possible, treatment should not be discontinued before a minimum of three to four weeks.

**Drug Interactions**
When TEVA-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.

When TEVA-TAMOXIFEN is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring.

The use of tamoxifen citrate in combination with an aromatase inhibitor as adjuvant therapy has not shown improved efficacy compared with tamoxifen citrate alone.

The known principal pathway for tamoxifen citrate metabolism in humans is demethylation catalysed by CYP3A4 enzymes. A pharmacokinetic interaction with the CYP3A4 inducing agent rifampicin, involving a reduction in tamoxifen plasma levels has been reported in the literature. Chronic use of CYP2D6 inhibitors can lead to reduced plasma concentrations of an active metabolite. Reduced efficacy on tamoxifen citrate has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) (see WARNINGS).

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen), has been reported in the literature. The relevance of this to clinical practice is not known.

**Pediatric Use**
The use of TEVA-TAMOXIFEN is not recommended in children, as safety and efficacy have not been established.

**Nursing Mothers**
It is not known if tamoxifen citrate is excreted in human milk and, therefore, the drug is not recommended during lactation. The decision either to discontinue nursing or
discontinue TEVA-TAMOXIFEN should take into account the importance of the drug to the mother.

**Effect on Ability to Drive and Use Machinery**
Tamoxifen citrate is unlikely to impair the ability of patients to drive or operate machinery. However, fatigue and asthenia have been reported with the use of tamoxifen citrate and caution should be observed when driving or operating machinery while such symptoms persist.

**ADVERSE REACTIONS**
Side effects can be classified as either due to the pharmacological action of the drug, e.g., hot flushes, vaginal discharge, pruritus vulvae, or those requiring further investigations, such as vaginal bleeding (to exclude the possibility of endometrial malignancy) and tumour flare (to exclude the possibility of progressive disease). Side effects can also be classified as more general in nature such as gastrointestinal intolerance (including such events as nausea, vomiting, constipation and diarrhea), headache, light-headedness and occasionally fluid retention and alopecia. When such side effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dose range) without loss of control of the disease.

Skin rashes (including rare reports of erythema multiforme, Stevens-Johnson syndrome, cutaneous vasculitis, and bullous pemphigoid) and commonly hypersensitivity reactions, including angioedema have been reported.

Increased bone and tumour pain and also local disease flare have occurred. These are sometimes associated with a good tumour response. Patients with soft tissue disease may have sudden increases in the size of pre-existing 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 citrate and generally subside rapidly. Uncommonly, patients with bony metastases have developed hypercalcaemia on initiation of therapy (see PRECAUTIONS).

Cataracts and retinopathy have been commonly reported in association with the administration of tamoxifen citrate (see WARNINGS). Other visual disturbances include retinal crystals, macular edema, keratopathy, and rare reports of corneal changes. Rare cases of optic neuropathy and optic neuritis have been reported in patients receiving tamoxifen citrate and, in a small number of cases, blindness has occurred.

Paraesthesia (tingling, pricking and numbness of skin) has been commonly reported in patients receiving tamoxifen citrate. Dysgeusia (taste loss and perversion) has been uncommonly reported in patients receiving tamoxifen citrate.

Decreases in platelet counts, usually only to 80,000 - 90,000 per cu mm but occasionally lower, have been uncommonly reported in patients taking tamoxifen citrate.
There have been uncommon reports of leucopenia and/or thrombocytopenia, sometimes in association with anemia. Neutropenia, including cases of agranulocytosis, have also been reported on rare occasions.

There is evidence of an increased incidence of ischemic cerebrovascular and thromboembolic events, including deep vein thrombosis and pulmonary embolism, occurring commonly during tamoxifen citrate therapy (see WARNINGS). An increased incidence of microvascular thrombosis has also been reported in women treated with tamoxifen citrate undergoing delayed microvascular breast reconstruction (see WARNINGS).

In the prevention setting, treatment with tamoxifen citrate has been associated with an increased risk of stroke (see WARNINGS). When tamoxifen citrate is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

Myalgia has been reported commonly in patients receiving tamoxifen citrate. In these cases, discontinuation of treatment resulted in resolution of symptoms.

Elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyl transeptidase (GGT) levels has been reported commonly during tamoxifen citrate therapy. On occasion, severe liver diseases have occurred from which some patients taking tamoxifen have died. Liver abnormalities reported include fatty liver, cholestasis and hepatitis, liver failure, cirrhosis, and hepatocellular injury (including hepatic necrosis). Occasionally, cases of hepatic cyst and peliosis hepatitis have also been reported.

Uncommon incidences of endometrial cancer and rare instances of uterine sarcoma (mostly malignant mixed Mullerian tumours) have been reported in association with tamoxifen citrate treatment (see WARNINGS and PRECAUTIONS).

Cutaneous lupus erythematosus and porphyria cutanea tarda have been observed rarely in patients receiving tamoxifen citrate. In these cases, discontinuation of treatment resulted in resolution of symptoms.

Fatigue and asthenia have been reported very commonly in patients taking tamoxifen citrate.

Other adverse reactions which are seen infrequently are depression and distaste for food.

Unless specified, the following frequency categories were calculated from the number of adverse events reported in the control arm of a large phase III study conducted where 3094 postmenopausal women patients with operable breast cancer were treated for 5 years with tamoxifen citrate and where no account was taken of whether the investigator considered it to be related to the study medication.
<table>
<thead>
<tr>
<th>Frequency</th>
<th>System Organ Class (SOC)</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥10%)</td>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>General disorder and administrative site conditions</td>
<td>Fatigue/Asthma</td>
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<tr>
<td></td>
<td>Metabolism and nutrition</td>
<td>Fluid retention</td>
</tr>
<tr>
<td></td>
<td>Reproductive system and breast</td>
<td>Vaginal bleeding</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue</td>
<td>Vaginal discharge</td>
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<tr>
<td></td>
<td>Vascular</td>
<td>Skin Rash</td>
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<tr>
<td></td>
<td>Blood and lymphatic system</td>
<td>Hot flushes</td>
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<tr>
<td>Common (≥1% and &lt;10%)</td>
<td>Eye disorders</td>
<td>Anemia</td>
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<tr>
<td></td>
<td>Immune system disorders</td>
<td>Cataracts</td>
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<td></td>
<td>Investigations</td>
<td>Retinopathy</td>
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<td></td>
<td>Musculoskeletal and connective tissue</td>
<td>Hypersensitivity reactions</td>
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<tr>
<td></td>
<td>Neoplasms benign, malignant and unspecified</td>
<td>Elevated triglycerides</td>
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<td></td>
<td>Nervous system</td>
<td>Leg cramp</td>
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<td></td>
<td>Reproductive system and breast</td>
<td>Myalgia</td>
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<td></td>
<td>Skin and subcutaneous tissue</td>
<td>Uterine fibroids</td>
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<td></td>
<td></td>
<td>Tumour Flare*</td>
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<tr>
<td></td>
<td></td>
<td>Ischaemic cerebrovascular events</td>
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<tr>
<td></td>
<td></td>
<td>Headache</td>
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<td>Light headedness</td>
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<td></td>
<td></td>
<td>Paraesthesia</td>
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<tr>
<td></td>
<td></td>
<td>Pruritus vulvae</td>
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<tr>
<td></td>
<td></td>
<td>Endometrial changes (including hyperplasia and polyps)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alopecia</td>
</tr>
<tr>
<td>Frequency</td>
<td>System Organ Class (SOC)</td>
<td>ADR</td>
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<td>--------------------</td>
<td>------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
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<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>• Vomiting</td>
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<td></td>
<td></td>
<td>• Diarrhoea</td>
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<tr>
<td></td>
<td></td>
<td>• Constipation</td>
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<tr>
<td></td>
<td>Hepatobiliary disorders</td>
<td>• Changes in liver enzymes</td>
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<tr>
<td></td>
<td></td>
<td>• Fatty liver</td>
</tr>
<tr>
<td></td>
<td>Multiple SOC Terms</td>
<td>• Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Blood and lymphatic system</td>
<td>• Thrombocytopenia</td>
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<tr>
<td>(≥ 0.1% and &lt;1%)</td>
<td></td>
<td>• Leucopenia</td>
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<tr>
<td></td>
<td></td>
<td>• Pancytopenia</td>
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<td></td>
<td>Eye disorders</td>
<td>• Visual disturbances</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>• Pancreatitis</td>
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<tr>
<td></td>
<td>Metabolism and nutrition</td>
<td>• Hypercalcaemia (in patients with bony metastases)</td>
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<td></td>
<td>Neoplasms benign, malignant and unspecified</td>
<td>• Endometrial cancer</td>
</tr>
<tr>
<td></td>
<td>Nervous system</td>
<td>• Dysgeusia</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>• Interstitial pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Hepatobiliary disorders</td>
<td>• Cirrhosis of the liver</td>
</tr>
<tr>
<td>Rare</td>
<td>Blood and lymphatic system disorders</td>
<td>• Neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(≥ 0.01% and &lt;0.1%)</td>
<td></td>
<td>• Agranulocytosis&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Eye disorders</td>
<td>• Corneal changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Optic neuropathy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>• Uterine Sarcoma (mostly malignant mixed Mullerian tumours)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Reproductive system and breast disorders</td>
<td>• Vaginal polyps&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• Endometriosis&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>• Cystic ovarian swelling&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Sympotms and treatment of overdosage

Acute overdosage in humans has not been reported. Possible overdosage effects might include hot flashes, nausea, vomiting and vaginal bleeding. No specific treatment for overdosage is known and treatment must be symptomatic.

In the case of accidental ingestion by a child, gastric emptying is suggested.

There have been reports in the literature that tamoxifen citrate given at several times the standard dose may be associated with prolongation of the QT interval of the ECG.

For management of a suspected drug overdose, contact your regional Poison Control Center.

Table 1  Adverse Drug Reactions (ADR) seen with Tamoxifen Citrate

<table>
<thead>
<tr>
<th>Frequency</th>
<th>System Organ Class (SOC)</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td></td>
<td>• Optic neuritis</td>
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<td>Hepatobiliary disorders</td>
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<td>• Hepatitis</td>
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<td>• Cholestasis</td>
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<td>• Hepatic failure</td>
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<td>• Hepatocellular injury</td>
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<td>• Hepatic necrosis</td>
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<td>Skin and subcutaneous tissue</td>
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<td>• Angioedema</td>
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<td>• Steven-Johnsons syndrome</td>
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<td>• Cutaneous vasculitis</td>
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<td>• Bullous pemphigoid</td>
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<td></td>
<td>• Erythema multiforme</td>
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<td>Skin and subcutaneous tissue</td>
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<td>• Cutaneous lupus erythematosus</td>
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<td>Congenital, familial and genetic disorders</td>
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<td>• Porphyria cutanea tarda</td>
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* Adverse event rates may not apply to premenopausal women or women treated for locally advanced or metastatic disease.

\[a\] Exact frequency not known but known to occur at $\leq 0.1\%$ from the ATAC study (A Randomized, Double-Blind Trial Comparing ARIMIDEX to NOLVADEX).

\[b\] The event was not observed in other major clinical studies. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size of 13,357 patients in the major clinical studies). This is calculated as $3/13,357$ which equates to a frequency category of ‘rare’.
DOSAGE AND ADMINISTRATION
The recommended daily dose of TEVA-TAMOXIFEN (tamoxifen citrate) is 20 to 40 mg in a single or two divided doses. The lowest effective dose should be used. In early disease, the recommended duration of therapy is 5 years. The optimal duration of therapy remains to be determined.

Pediatric Use: The use of TEVA-TAMOXIFEN is not recommended in children, as safety and efficacy have not been established.

AVAILABILITY
Film Coated Tablets
10 mg: White to off-white, round, bi-convex, film coated tablets, engraved stylized "N" over 10 on one side and plain on the other side, containing tamoxifen citrate equivalent to 10 mg of tamoxifen. These tablets are available in bottles of 60, 100 and 250 and in blister packages of 6 strips of 10 tablets.

20 mg: White to off-white, round, bi-convex, film coated tablets, engraved on one side stylized "N" over scoreline, 20 under it, and plain on the other, containing tamoxifen citrate equivalent to 20 mg of tamoxifen. These tablets are available in bottles of 60 and 100 and in blister packages of 3 strips of 10 tablets.
INFORMATION FOR THE CONSUMER

TEVA-TAMOXIFEN
(Tamoxifen Citrate)
10 and 20 mg Tablets, BP

DESCRIPTION
Tamoxifen is a medicine that blocks the effects of the hormone estrogen in the body. It is used to treat breast cancer.

The exact way that tamoxifen works against cancer is not known, but it may be related to the way it blocks the effects of estrogen on the body.

Tamoxifen is available only with your doctor's prescription.

WHAT DOES TEVA-TAMOXIFEN CONTAIN?
10mg and 20mg Film Coated Tablets: The core tablet is composed of mannitol, povidone, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. The film coating is composed of hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

BEFORE USING THIS MEDICATION
In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This is a decision you and your doctor will make.

Before taking tamoxifen, tell your doctor if any of the following apply to you:

- If you have ever had any unusual or allergic reaction to tamoxifen or any one of its ingredients (See What Does TEVA-TAMOXIFEN Contain?).

- If you intend to become pregnant. It is best to use some kind of birth control while you are taking tamoxifen and for about two months after you stop taking it. Please see your doctor for advice on what contraceptive precaution you should take, as some may be affected by tamoxifen. Tell your doctor right away if you think you have become pregnant while taking tamoxifen or within two months of having stopped it.

- It is important that you tell your doctor immediately if you have any unusual vaginal bleeding or other gynecological symptoms (such as pelvic pain or pressure) when you are taking tamoxifen or anytime afterwards. This is because a number of changes to the lining of the womb (the endometrium) may occur, some of which may be serious and could include cancer.

- If you are breastfeeding or intend to breastfeed.
• If you are taking or have recently taken any other prescription including antidepressants such as paroxetine (to improve mood or symptoms of hot flushes), or over-the-counter medicine.

• If you have any other medical problems, especially cataracts (or other eye problems) or low blood cell counts.

• If you have a history of blood clots, including deep vein thrombosis (a blood clot in one of the deep veins of the body - usually within the leg) or are taking anticoagulants such as warfarin (to prevent blood clots).

• Tamoxifen should not be taken with aromatase inhibitors, such as anastrozole, letrozole or exemestane.

• If you are going to have a breast reconstruction operation where your own tissue is moved to shape a new breast and this occurs weeks to years after the primary cancer operation, tamoxifen citrate may increase your risk of complications, including complete loss of the new tissue.

• If you have a history of pulmonary embolism (obstruction of a pulmonary artery by foreign matter such as fat, air, tumor tissue or a blood clot).

• If you have a history of stroke.

• If you go into the hospital, let medical staff know you are taking tamoxifen.

YOU SHOULD NOT TAKE TEVA-TAMOXIFEN IF:
• You have ever had an unusual or allergic reaction to TEVA-TAMOXIFEN or any one of its ingredients (See What Does TEVA-TAMOXIFEN Contain?)
• You are pregnant.

TEVA-TAMOXIFEN should not be given to children.

PROPER USE OF THIS MEDICATION
Use this medication only as directed by your doctor. Do not use more or less of it and do not use it more often than your doctor ordered. Taking too much may increase the chance of side effects, while taking too little may not improve your condition.

Tamoxifen sometimes causes nausea and vomiting. However, it may have to be taken for several weeks or months to be effective. Even if you begin to feel ill, do not stop using this medicine without first checking with your doctor. Ask your health care professional for ways to lessen these effects.

Missed dose - If you miss a dose, take the dose as soon as you remember. Do not take two doses at the same time.
TO STORE THIS MEDICINE

- KEEP OUT OF THE REACH OF CHILDREN.
- Store at room temperature (15 to 30°C) and keep away from direct light.
- Do not store in damp places. Heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed.

PRECAUTIONS WHILE USING THIS MEDICINE

It is important to use some type of birth control while you are taking tamoxifen. Please see your doctor for advice on what contraceptive precautions you should take, as some may be affected by tamoxifen. Tell your doctor right away if you think you have become pregnant while taking this medicine or within two months of stopping it.

Driving and using machines: Tamoxifen citrate tablets are unlikely to affect your ability to drive a car or to operate machinery. However, tiredness and weakness have been reported with the use of tamoxifen citrate and caution should be observed when driving or operating machinery while such symptoms persist.

SIDE EFFECTS OF THIS MEDICINE

Along with its needed effect, a medicine may cause some unwanted effects. Some side effects will have signs or symptoms that you can see or feel. Your doctor will watch for others by doing certain tests.

Also, because of the way this medicine acts on the body, there is a chance that it might cause other unwanted effects that may not occur until months or years after the medicine is used. Tamoxifen has been reported to increase the risk of cancer of the endometrium or uterus (womb) as well as uterine fibroids (non-cancerous tumours) in some women taking it. It may also cause a drop in some of your blood cell counts, thrombocytopenia (bruising), an increased risk of blood clots and stroke, hypertriglyceridemia, pancreatitis, jaundice and ovarian cysts. In addition, tamoxifen citrate has been reported to cause cataracts and other eye problems. Discuss these possible effects with your doctor.

Check with your doctor or pharmacist as soon as possible if any of the following side effects occur:

Do not be alarmed by this list of possible events. You may not have any of them.

- Hot flushes
- Discomfort in the pelvis
- Vaginal bleeding
- Itching around the vagina
- Vaginal discharge
- Stomach upsets (including nausea, vomiting, diarrhea and constipation)
- Headaches
- Light-headedness
- Sensory changes (including taste disorder and numbness or tingling in the skin)
- Fluid retention (possibly seen as swollen ankles)
- Low platelet counts (thrombocytopenia)
- Low white blood cell counts (leucopenia) or decrease of specific white cells (neutropenia and agranulocytosis)
- Decrease in red blood cells (anemia)
- Pain or tenderness in upper abdomen
- Skin rash or itching or peeling skin
- Inflammation of small blood vessels in the skin leading to skin rash
- Hair loss
- Changes in blood tests of liver function. On occasion more severe liver diseases have occurred from which some patients have died. These liver diseases include inflammation of the liver, liver cirrhosis, liver cell damage, formation of fatty liver cells, reduced bile formation, and failure of the liver. Symptoms may include a general feeling of being unwell, with or without jaundice (yellowing of the skin and eyes)
- Disturbances of vision or difficulties in seeing properly (possibly due to cataracts, changes to the cornea or disease of the retina)
- Cases of optic nerve diseases have been reported and, in a small number of cases, blindness has occurred
- Breathlessness and cough (inflammation of the lungs)
- Pain, swelling or redness of the calf or leg which may indicate a blood clot
- Chest pain or shortness of breath which may indicate a blood clot
- Leg cramps
- Muscle pain
- Non-cancerous mass in the inner lining of the vagina (called vaginal polyp)
- Inflammation of the skin characterized by rash or erythema, very often on areas exposed to light (a condition called cutaneous lupus erythematosus)
- A skin condition characterized by skin blisters in areas exposed to the light, (a condition called porphyria cutanea tarda)
- Sudden onset of weakness or paralysis of the arms or legs, sudden difficulty walking or talking, difficulty in holding things or difficulty in thinking, any of which may occur because the blood supply in the blood vessels of the brain is reduced (these could be symptoms of a stroke)
- At the beginning of treatment, a worsening of the symptoms of your breast cancer such as an increase in pain and/or an increase in the size of the affected tissue may occur. In addition, if you experience excessive nausea, vomiting and thirst, you should tell your doctor. This may indicate possible changes in the amount of calcium in your blood and your doctor may have to do certain blood tests.
- Tiredness and weakness

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.
STOP TAKING TEVA-TAMOXIFEN and contact your doctor immediately in any of the following situations:

- If you develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.
- If you develop swelling of the face, lips, tongue, and/or throat which may cause difficulty swallowing.
- If you develop swelling of the hands, feet or ankles.
- If you develop "nettle rash" or "hives" (urticaria).

If you need further information ask your doctor or pharmacist.

In case of accidental overdose, consult a physician immediately or contact your regional Poison Control Centre.

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<th>Reporting Side Effects</th>
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<td>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</td>
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3 ways to report:
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited
at: 1-800-268-4127 ext. 1255005 (English Canada)
or druginfo@tevacanada.com

or 1-877-777-9117 (French Canada)

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

Last revised: July 16, 2015
PHARMACEUTICAL INFORMATION

Trade Name: TEVA-TAMOXIFEN

Common Name: Tamoxifen Citrate

TEVA-TAMOXIFEN is the trans isomer of a triphenylethylene derivative.

Structural Formula:

\[
\text{(CH}_3\text{)_3NCH}_2\text{CH}_2\text{O} \quad \begin{array}{c}
\text{C}=\text{C} \\
\end{array} \quad \text{C}_2\text{H}_5 \\
\text{HO} \quad \text{C} \quad \text{COOH} \\
\text{CH}_2\text{COOH} \quad \text{CH}_2\text{COOH}
\]

Molecular Formula: \( C_{26}H_{29}NO \quad C_6H_8O_7 \)  
Molecular Weight: 563.62

Chemical Name: \((Z)-2-\{4-(1,2\text{-diphenyl}-1\text{-butenyl})\text{phenoxy}\}-\text{N,\text{N}}\text{-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1).}

Description: Tamoxifen citrate is a fine, white, essentially odourless, crystalline powder with a melting point range between 142.0°C and 144.5°C. It is hygroscopic and photosensitive.

Composition:
10mg and 20mg Film Coated Tablets:
The core tablet is composed of mannitol, povidone, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate. The film coating is composed of hydroxypropyl methylcellulose, polyethylene glycol and titanium dioxide.

STABILITY AND STORAGE RECOMMENDATIONS
TEVA-TAMOXIFEN should be stored at room temperature (15 to 30°C) and protected from light.

PHARMACOLOGY

Pharmacokinetics and Metabolism
Preliminary pharmacokinetics in women using radiolabeled tamoxifen citrate has shown that most of the radioactivity is slowly excreted in the feces while 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 levels of 0.06 to 0.14 µg/mL at 3 to 7 hours after dosing, with only 20 to 30% of the drug present as tamoxifen citrate. The initial half-life was 7 to 14 hours, with secondary peaks 4 or more days later. The prolongation of blood levels and fecal excretion is believed to be due to enterohepatic circulation.

**Antiestrogenic Effect**

In those species where tamoxifen is an estrogen antagonist, this property is manifest in various ways. Thus in spayed rats, vaginal cornification in response to the daily subcutaneous injection of estradiol can be prevented by concomitant oral dosing with tamoxifen citrate and in immature rats the uterotrophic effect of estrogen can be similarly inhibited.

Also in rats, tamoxifen citrate will terminate early pregnancy by preventing implantation of the blastocysts. It is known in rats, estrogen secreted by the ovaries on day 4 of pregnancy initiates implantation (on day 5). There is evidence that, at the lowest dose needed to prevent implantation, tamoxifen citrate acts by counteracting this estrogen. In normal female rats having regular estrous cycles, ovulation can be delayed by administration of a single dose of tamoxifen citrate given on or before the day of diestrous. In the rat (and other spontaneously ovulating species), it appears that the ovulatory discharge of luteinizing hormone (LH) from the pituitary is "triggered" by the action of estrogen on the hypothalamus and/or pituitary. The secretion of estrogen from the ovaries reaches a peak before this LH discharge. The inhibitory effect of tamoxifen citrate on ovulation is attributed to interference with the "feedback" action of estrogen at the hypothalamic and/or pituitary level.

In the pig-tailed monkey (*M. nemestrina*), the activity of tamoxifen as an estrogen antagonist is shown by its effect on the response to estrogen of the perineal region ("sexual skin"). Mature females of this species menstruate regularly at intervals of about 28 days. An edematous swelling of the "sexual skin" develops during the follicular phase of the cycle and subsides more rapidly at about the presumed time of ovulation. The swelling is due to endogenous estrogen and is not seen in the ovariectomized animals unless estrogen is given. In an ovariectomized pig-tail, large daily doses of tamoxifen citrate caused no swelling of the "sexual skin". On the other hand, the swelling induced by daily injection of estradiol was reduced almost to zero by small (oral) doses of tamoxifen citrate given at the same time.

Although the capacity of tamoxifen citrate (demonstrated in spayed rats and monkeys) to inhibit the response to estrogen suffices to explain its effects, outlined above, in intact animals of these species, the possibility that it may also inhibit the endogenous production of estrogen cannot yet be excluded.

In very large doses, tamoxifen citrate causes a limited increase in uterine weight and incomplete vaginal cornification in spayed rats, indicating that it has some degree of
estrogenic activity. In one species, the mouse, it behaves as an estrogen without demonstrable estrogen antagonistic activity at any dose.

**TOXICOLOGY**
Tamoxifen citrate has a low acute toxicity in all species studied, including mice, rats, rabbits and marmosets. The acute oral LD$_{50}$ is greater than 1 g/kg in all species treated.

Chronic toxicity studies were conducted in rats, dogs and marmosets. In the 3 month rat study, tamoxifen citrate was administered daily at doses of 2, 20, and 100 mg/kg as a mixture containing approximately 10% of the corresponding cis-isomer, an estrogen. The changes induced were reduction in weight of ovaries, testes, seminal vesicles, and ventral prostate when related to body weight. Decreased numbers of corpora lutea and follicular cysts, as well as reduction in uterine size, were noted.

The endometrium of all dosed rats showed a complete absence of glands, the epithelium consisting of a single layer of columnar cells with small areas of flattening and occasional squamous metaplasia. The endometrial stroma was somewhat condensed giving it a more fibrous appearance.

High-dose male rats showed cessation of maturation of spermatozoa. Seminiferous epithelium showed scattered necrotic cells. A similar, but less severe change, was seen in males receiving the intermediate dose. The testes in rats which received a low dose showed reduced numbers of spermatoocytes and occasional atrophic tubules.

A few treated rats showed a marginal increase in the height of the thyroid epithelium and all treated rats showed a thin zone of adrenal cortical congestion and edema.

In a 6 month rat study tamoxifen citrate was administered orally at doses of 0.05 mg, 0.8 mg, 2.4 mg, 4.8 mg and 9.6 mg/kg. Changes produced by tamoxifen were observed mainly in rats treated with 2.4, 4.8 and 9.6 mg/kg. The reproductive organs showed severe atrophic changes increasing with dose from 2.4 to 9.6 mg/kg. Serum alkaline phosphatase and sodium levels were raised and alanine aminotransferase, aspartate aminotransferase and albumin levels were lowered.

No significant histological findings were observed in the liver.

In a 2 year carcinogenicity study, rats received 5, 20 and 35 mg/kg tamoxifen by gavage (all of which represent significant multiples of the recommended human dose of 20 - 40 mg/day). Hepatocellular carcinomas were reported at all doses. The incidence of these tumours was greater among rats given 20 or 35 mg/kg/day (69%) than those given 5 mg/kg/day (14%). In addition, there appears to be a dose related increase in cataracts.

In the 3 month dog study, doses of 1, 10, and 50 mg/kg were administered orally. The same cis-trans mixture was used as in the 3 month rat study. The treated males in all groups showed a decrease in weight of the testes and pituitary. The females showed an increase in weight of the uterus. Histological observations were as follows:
The testes were atrophic in all dosed dogs. The seminiferous epithelium in most tubules comprised only a layer of spermatogonia and Sertoli cells. There was a considerable increase in the fibrous stroma around the tubules due to the condensation of the normal interstitial tissue as a result of atrophy. This change was attributed to the "estrogenic" effect of the cis-trans mixture.

The ovaries of the dosed females showed reduced numbers of follicles, cessation of ovulation, and hyperplasia of the germinal epithelium. This last change is an exaggeration of the physiological changes seen in metestrus. These changes were less marked in the dogs receiving the lower doses.

In the uterus of all dosed females, there was squamous metaplasia of the endometrium with severe endometritis. The myometrium showed separation of the muscle bundle by a markedly edematous connective tissue which resulted in an "attenuated" appearance of the muscle. However, it was unlikely that there was an alteration in the total bulk of the muscle.

The livers of three males and one female in the highest dosage group showed bile plugs in the bile canaliculi and pigment in the Kupffer cells. The liver was normal apart from slight thinning of the cell cords. These findings are in keeping with the biochemical observation of raised serum alkaline phosphatase. It should be remembered that the dose in this case is 500 times that required to prevent implantation in the dog. All other organs were within normal limits.

Chronic dosing in the marmoset involved one 6 month study. Tamoxifen citrate was administered orally at doses of 0.8, 4.0 and 8.0 mg/kg. The only treatment related, pathologically significant effect due to dosing was the formation of cystically enlarged follicles in the ovaries of the females treated at 8.0 mg/kg.

An additional study of two months duration was conducted in rats where the activity of tamoxifen was compared with that of pure cis-isomer and pure trans-isomer at an oral dose of 20 mg/kg. The reproductive tissue changes were similar to those listed above for all treatment groups, but the adrenal and thyroid lesions were seen only in those rats which received the cis-isomer.

A reversibility test was conducted in female rats using tamoxifen citrate administered orally at doses of 0.5 and 2.0 mg/kg for three months; one-third of the animals were held without drug for an additional three months. Changes similar to those described above were noted in ovaries and uteri after 3-months dosing. These were not present in rats held an additional three months without dosing with tamoxifen citrate.

A reversibility study was conducted in female dogs in which tamoxifen citrate was compared with stilbestrol and clomiphene. Tamoxifen citrate was administered at a dose of 0.1 mg/kg for three months with one animal out of four left untreated for an additional month to test for reversibility.
Squamous metaplasia was not present in the uterus of dogs dosed with tamoxifen citrate. In the myometrium, there was a diminution of collagen with fragmentation of the bundles. The muscle bundles were separated by edema. Withdrawal of tamoxifen citrate produced an effect similar to a mild estrogenic change with increased collagen in thick bundles. The ovaries showed cessation of ovulation and slight hyperplasia of the germinal epithelium.

The studies comparing tamoxifen citrate with conventional estrogens showed the estrogenic activity of tamoxifen in mice was responsible for gonadal tumours. Chronic studies in mice included an initial 15-month study where the cis-trans mixture described above was administered orally at doses of 5 and 50 mg/kg. This was followed by a 13 month study where the pure cis and trans forms were compared with the cis-trans mixture at a dose of 20 mg/kg and with stilbestrol and ethinyl estradiol. An additional study of 14 months was conducted using a dose of 0.1 mg/kg to investigate the effects of lower doses of the cis, trans, and cis-trans mixture of tamoxifen citrate with stilbestrol and ethinyl estradiol. Interstitial cell tumours of the testes and granulosa cell tumours of the ovary were found and were compound related. After six months of treatment, the mice developed a spinal deformity with kyphosis. The lesion was characterized as elongation of vertebral bodies. In addition, there was increased opacity of long bone due to ossification of the medullary cavity. Some of these can be attributed to estrogenic activity; others were of unknown etiology and did not occur at lower doses.

A series of three tests were conducted to evaluate the ocular toxicity of tamoxifen citrate as compared to compounds which caused ocular lesions and have a similar chemical structure such as clomiphene and triparanol. In the first two tests, female rats were mated and treated with tamoxifen citrate, clomiphene or clomiphene B on day 11 of pregnancy and killed on day 19 or 20. In addition to observations on the uterine and fetal changes, the eyes of the fetuses were examined histologically. In the third experiment, the pregnant females were given clomiphene on day 11 of pregnancy and the fetuses delivered by cesarean section on day 22.

They were immediately fostered to control animals and allowed to develop to weaning, when they were killed and examined for cataracts. The results of the first two studies showed no significant increase in embryonic or fetal deaths in any of the treatment groups. Hydramnios was observed in treated rats together with an increase in placental weight and a decrease in uterine weight. Fetal cataracts were observed with clomiphene and clomiphene B, but not with tamoxifen citrate. The incidence of cataracts induced by clomiphene in fostered neonates in the third test was 9.5%.

Teratogenic studies were conducted in rats and rabbits. Since tamoxifen citrate inhibits implantations, some difficulties were encountered in these studies. Doses in rats ranged from 0.02 to 4.0 mg/kg orally and in rabbits from 0.01 to 2.0 mg/kg (administered in the feed). The only drug-induced abnormality which was detected occurred in rats and consisted of a reversible rib deformity which, under certain conditions, had an incidence as high as 50%.
Evidence is presented which suggests that the cause of the deformity is mechanical due to the failure of uterine growth caused by the antiestrogenic property of the compound.

Tamoxifen citrate is not mutagenic in a range of in vitro and in vivo mutagenicity studies.

Tamoxifen citrate was genotoxic in some in vitro tests and in vivo genotoxicity tests in rodents.

ESTROGEN RECEPTOR ASSAY

Introduction
Recently, studies in estrogen-dependent tissues have led to the discovery of a cytoplasmic protein which binds estrogen with high affinity and specificity. Estrogen enters the cytoplasm of all cells whether or not they are estrogen-dependent. However, in the cytoplasm of estrogen-dependent cells are found specific protein molecules that are termed receptors. These receptor proteins bind estrogen biologically with great affinity and specificity. Following this initial binding step, the estrogen receptor complex undergoes an activation which allows the complex to enter the nucleus of the cell and bind to chromatin, the genetic information of the cell. Once bound to the chromatin, the interaction of the estrogen receptor complex with the genetic information of the cell leads to the elaboration of new species of messenger RNA.

These molecules are then released into the cytoplasm where they can be translated on polysomes into new proteins.

Antiestrogens are also able to enter the cytoplasm of the estrogen-dependent cell and bind biologically to the protein receptor with affinity and specificity, thus activating the complex to also translocate to the nucleus. However, the normal estrogen transcriptional processes are altered. Hence, antiestrogens interfere with estrogen-dependent tumor growth by competing with estrogens for the receptor site and by turning off the normal processes of the genetic information within the nucleus. Reports concerning the relationship between clinical responses of patients with breast cancer receiving endocrine therapy and the presence or absence of estrogen receptors have been compiled.

In patients with tumors positive for estrogen receptors, the response rate to endocrine therapy was approximately 56%; and in patients with tumors negative for estrogen receptors, the response rate was about 10%. It was concluded that estrogen receptor assays are useful in predicting the results of endocrine therapy in patients with breast cancer.

Methods
a. Dextran-Coated Charcoal Assay (DCC)

The Dextran-Coated Charcoal assay (DCC) involves the extraction of the highly labile estradiol receptor from a cytosol prepared from the tumor tissue. After incubating with tritiated estradiol, which interacts with the binding sites of receptors, the excess estradiol
is separated from the incubate with dextran-coated charcoal. The amount of non-specific binding (e.g., albumin) is then determined and the quantity of estradiol receptors in the tissue is estimated from the difference in the total binding less non-specific binding per milligram of protein. Tumors which show binding capacity similar to benign tumors are designated ER-negative, while those with higher binding capacity are designated ER-positive.

b. Sucrose Gradient Method (SG)

The weighed tumor specimen is immersed in liquid nitrogen and shattered. The residual tissue powder is homogenized with efficient cooling in four volumes of buffer, using a tissue disintegrator with two or three homogenization periods, each followed by a cooling period. The homogenate is centrifuged to precipitate the particulate matter. Two portions of the cytosol fraction are removed and treated with either buffer alone or buffer containing an agonist. When equilibrium is reached, tritiated estradiol is added to each mixture. After mixing and standing in the cold, a portion of each mixture is layered on a 10 to 30% sucrose gradient containing buffer, and centrifuged. Successive fractions are collected, from which the radioactivity is counted.

Receptor-positive tumor specimens exhibit 8S complex, whereas others show various amounts of specific binding in the 4S region as well. Radioactivity associated with the 8S form of estrophilin is estimated from the difference in the sedimentation curves, with and without inhibitor, from fraction 1 to the minimum observed around fractions 18 to 22, depending on the ultra-centrifugation. The 4S radioactivity is similarly calculated by difference of the curves between the minimum and the point where the curve with inhibitor crosses the curve without inhibitor.

Interpretation of Results

Laboratory results of the estrogen receptor assay should be interpreted by a qualified expert, as results may vary due to technique, handling and storage of the specimen, and the patient's menopausal status or recent drug therapy. Quantitative results vary among laboratories and methods. As a result of retrospective correlation made by various investigators based upon patients' responses to hormonal manipulation, a result of less than 3 fmol/mg of cytosol protein is considered ER-negative, 3 to 10 fmol/mg cytosol protein is equivocal and over 10 fmol/mg is considered ER-positive.

For a more detailed description of the analytic techniques and interpretation of results, the following references may be consulted.

ESTROGEN RECEPTOR MONOCLONAL ANTIBODIES

The quantitative determination of estrogen and progesterone receptors in human breast cancers has served as a guide to therapeutic invention as well as prognosis. Analysis of the receptor content of the primary tumor at the time of mastectomy is able to predict response to endocrine therapy should the tumor recur as well as estimating the probability and rapidity of recurrence. However, current methods for determination of estrogen and
progesterone receptors suffer from several deficiencies. They are costly in terms of laboratory time, they require a large sampling of tumor tissue, rapid receptor deterioration during specimen processing or storage can often lead to erroneous results and ligand-binding assays fail to detect receptor that is already complexed with non-radioactive hormone of endogenous or therapeutic origin. These limitations have led to investigation of improved techniques for a simple, accurate and inexpensive assay which will recognize the receptor whether or not it retains its ability to bind hormones.

Most recently monoclonal antibody technology has been used to generate a number of monoclonal antibodies specific for antigenic determinants on or near the estrogen receptor site. A number of antibodies have been produced by Greene and Jensen at the Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois.

These specific monoclonal antibodies recognize the extranuclear estrogen receptor of the MCF-7 human breast cancer cell line. These antibodies bind to nuclear and cytosolic estrogen receptors from a variety of tissues and are therefore unique and specific probes for examining the structure and function of the estrogen receptor. Three such antibodies (D58, D75, D547) have been described to recognize different antigenic determinants on the receptor molecule. A combination of two such antibodies can be used in a sandwich technique for the immunoradiometric (IRMA) or enzyme-linked immunosorbent (ELISA) determination of estrogen receptor. These three antibodies recognize estrogen receptors in human breast cancer specimens as well as estrogen receptor in uterine tissue from other species. Further studies with the D547 and D58 monoclonal antibodies have revealed that these antibodies can distinguish among various forms of the estradiol-estrogen receptor complex. The antigenic determinants recognized by these particular antibodies on breast tumor cytosolic receptors are not significantly altered by the binding of either estrogen or antiestrogen to the receptor. Studies such as this are able to demonstrate fundamental differences in the subcellular fate of the estrogen or antiestrogen-receptor complexes, and provide clues to the mechanism of action of estrogens and antiestrogens.

Poulsen has used two monoclonal antibodies specific for MCF-7 estrogen receptor to stain human breast cancer tissue sections using an immunoperoxidase technique. The immunoperoxidase staining was predominantly located in the nucleus of the malignant epithelial cells. No relationship between tumor type or degree of differentiation of invasive ductal carcinomas and staining features was observed. Poulsen found a significant positive correlation between the number of positively stained cells and cytosol receptor content. Similarly, King has developed monoclonal antibody D-5, an IgG1 which binds to soluble estrogen receptor in a dose-dependent manner. Antibody D-5 is specific for human soluble estrogen receptor and will not react with other steroid-binding proteins or nuclear estrogen receptor. King found a highly significant correlation between estrogen receptor content and D-5 reactivity in human breast cancer sections. Kodama has used similar techniques to study the expression of estrogen receptors of human breast cancer clonal growth using the soft-agar cloning assay. He found that estrogen receptor expression increased with clonal growth of tumor cells to colonies and that estrogen receptor appeared to be expressed in the differentiation process. Finally,
Dr. Edwards has developed a monoclonal antibody to the chicken oviduct progesterone receptor. This antibody also recognizes denatured human progesterone receptor as its antigen. Further applications of this monoclonal antibody are currently being examined.

The development of specific monoclonal antibodies directed at antigenic determinants of the estrogen or progesterone receptor will make it possible to more accurately and precisely define levels of estrogen or progesterone receptors in human tumor tissue. This technology will allow such assays to be performed on much smaller amounts of tumor tissue than are currently needed for standard receptor assays. In addition the future availability of standardized kits for performing monoclonal antibody assays will help provide uniformity when results of receptor levels are described.
MONOClonal antibody estrogen receptor references


ESTROGEN RECEPTOR REFERENCES


SELECTED BIBLIOGRAPHY


