PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr TEVA-TAMOXIFEN

Tamoxifen Citrate Tablets

Tablets, 10 mg and 20 mg, Oral

BP

Antineoplastic Agent

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RECENT MAJOR LABEL CHANGES

2 Contraindications	11/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-TAMOXIFEN (tamoxifen citrate) is indicated for:

- the adjuvant treatment of early breast cancer in women with estrogen receptor positive tumors.
- the treatment of women with hormone responsive locally advanced / metastatic breast cancer.

1.1 Pediatrics

Pediatrics (< 18 years of age): the use of TEVA-TAMOXIFEN is not recommended in children, as safety and efficacy have not been established.

2 CONTRAINDICATIONS

TEVA-TAMOXIFEN is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

TEVA-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 citrate, although no causal relationship has been established.

Women should be advised not to become pregnant while taking TEVA-TAMOXIFEN and for nine months following the cessation of therapy and should use a barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal 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 TEVA-TAMOXIFEN or within nine months of cessation of therapy.

When used in the prevention setting (an indication not approved in Canada), TEVA-TAMOXIFEN 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

With obvious disease progression, the drug should be discontinued. However, because an occasional patient will have a local disease flare 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 (see ADVERSE REACTIONS). There are data to suggest that, if possible, treatment should not be discontinued before a minimum of three to four weeks.

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.

4.2 Recommended Dose and Dosage Adjustment

The recommended daily dose of TEVA-TAMOXIFEN 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: Health Canada has not authorized an indication for pediatric use.

4.4 Administration

TEVA-TAMOXIFEN is for oral use only.

4.5 Missed Dose

If a patient misses a dose, they should take the next usual dose as soon as they remember. Do not take two doses at the same time.

5 OVERDOSAGE

Acute overdosage in humans has not been reported. Possible overdosage effects might include hot flushes, 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 centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Film coated tablets 10 mg, 20 mg	Colloidal silicon dioxide, hydroxypropyl methylcellulose, mannitol, magnesium stearate, povidone, polyethylene glycol, sodium starch glycolate and titanium dioxide.

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.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

TEVA-TAMOXIFEN should be used only for the conditions listed under the INDICATIONS section.

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) (see DRUG INTERACTIONS).

Carcinogenesis and Mutagenesis

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 TEVA-TAMOXIFEN. 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.

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 estrogenic properties of tamoxifen citrate. Any patients receiving TEVA-TAMOXIFEN or having previously received TEVA-TAMOXIFEN who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated.

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 citrate 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.

Hepatocellular carcinomas have been reported in a 2 year oncogenicity study in rats receiving tamoxifen citrate (see NON-CLINICAL TOXICOLOGY). In addition, gonadal tumors have been

reported in mice receiving tamoxifen citrate in long-term studies (see NON-CLINICAL TOXICOLOGY). The clinical relevance of these cancer findings has not been established.

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 citrate. No causal link has been established and the clinical significance of these observations remains unclear.

Cardiovascular
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 TEVA-TAMOXIFEN for the prevention of breast cancer is not an approved indication in Canada.

Driving and Operating Machinery
TEVA-TAMOXIFEN 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.

Endocrine and Metabolism
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 tamoxifen citrate 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.

Hematologic
TEVA-TAMOXIFEN should be used cautiously in patients with existing thrombocytopenia or leukopenia. Decreases in platelet counts, usually to 80,000 - 90,000/mm_3, 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.

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. Complete blood counts, including platelet counts, should be obtained periodically.

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 (see Drug-Drug Interactions). For treatment of breast cancer, the risks and benefits of TEVA-TAMOXIFEN should be carefully considered in women with a history of thromboembolic events.

As tamoxifen citrate has been associated with increased rates of thromboembolic events, TEVA-TAMOXIFEN 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 TEVA-TAMOXIFEN before undergoing delayed microvascular breast reconstruction after a careful individual benefit/risk assessment.

When TEVA-TAMOXIFEN is co-administered with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur (see Drug-Drug Interactions).

Hepatic/Biliary/Pancreatic
Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) levels have 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 (see ADVERSE REACTIONS). Monitoring liver function tests during treatment with TEVA-TAMOXIFEN is recommended.

Immune
Hypersensitivity reactions including rare reports of erythema multiforme, Stevens-Johnson syndrome, cutaneous vasculitis, bullous pemphigoid and angioedema have been reported (see ADVERSE REACTIONS).

Monitoring and Laboratory Tests
Estrogen and progesterone receptors status should be determined by a laboratory using a validated test.

Musculoskeletal
Myalgia has been reported commonly in patients receiving tamoxifen citrate. In these cases, discontinuation of treatment resulted in resolution of symptoms (see ADVERSE REACTIONS).

Ophthalmologic
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.

Visual disturbances include retinal crystals, macular edema, keratopathy, and rare reports of corneal changes have occurred. Rare cases of optic neuropathy and optic neuritis have been reported in patients receiving tamoxifen and, in a small number of cases, blindness has occurred (see ADVERSE REACTIONS). Patients should be advised to seek medical attention if they experience any visual disturbances.

Sexual Function/Reproduction
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.

7.1 Special Populations

7.1.1 Pregnant Women

TEVA-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 citrate, although no causal relationship has been established (see CONTRAINDICATIONS).

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): the use of TEVA-TAMOXIFEN is not recommended in children, as safety and efficacy have not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Frequency	System Organ Class (SOC)	ADR
Very common (≥10%)	Gastrointestinal disorders	• Nausea
	General disorder and administrative site conditions	• Fatigue/Asthenia
	Metabolism and nutrition	• Fluid retention
	Reproductive system and breast	• Vaginal bleeding
		• Vaginal discharge
	Skin and subcutaneous tissue	• Skin Rash
	Vascular	• Hot flushes
Common (≥1% and <10%)	Blood and lymphatic system	• Anemia
	Eye disorders	• Cataracts
		• Retinopathy
	Immune system disorders	• Hypersensitivity reactions
	Investigations	• Elevated triglycerides
	Musculoskeletal and connective tissue	• Leg cramp
		• Myalgia
	Neoplasms benign, malignant and unspecified	• Uterine fibroids
		• Tumour Flare[a]

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

Frequency	System Organ Class (SOC)	ADR
	Nervous system	• Ischaemic cerebrovascular events
		• Headache
		• Light headedness
		• Paraesthesia
	Reproductive system and breast	• Pruritus vulvae
		• Endometrial changes (including hyperplasia and polyps)
	Skin and subcutaneous tissue	• Alopecia
	Gastrointestinal disorders	• Vomiting
		• Diarrhoea
		• Constipation
	Hepatobiliary disorders	• Changes in liver enzymes
		• Fatty liver
	Multiple SOC Terms	• Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)

* 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 ≤ 0.1% from the ATAC study (A Randomized, Double-Blind Trial Comparing anastrozole to tamoxifen citrate).

Skin rashes and commonly, hypersensitivity reactions have been reported.

Cataracts and retinopathy have been commonly reported in association with the administration of tamoxifen citrate (see WARNINGS AND PRECAUTIONS).

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

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 AND PRECAUTIONS). An increased incidence of microvascular thrombosis has also been reported in women treated with tamoxifen citrate undergoing delayed microvascular breast reconstruction (see WARNINGS AND PRECAUTIONS).

In the prevention setting, treatment with tamoxifen citrate has been associated with an increased risk of stroke (see WARNINGS AND PRECAUTIONS). 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. 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. 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.

Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT) levels have 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.

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

8.3 Less Common Clinical Trial Adverse Reactions

Table 2 Adverse Drug Reactions (ADR) seen with Tamoxifen Citrate*

Frequency	System Organ Class (SOC)	ADR
Uncommon (≥ 0.1% and <1%)	Blood and lymphatic system	• Thrombocytopenia • Leucopenia • Pancytopenia
	Eye disorders	• Visual disturbances
	Gastrointestinal disorders	• Pancreatitis
	Metabolism and nutrition	• Hypercalcaemia (in patients with bony metastases)
	Neoplasms benign, malignant and unspecified	• Endometrial cancer
	Nervous system	• Dysgeusia
	Respiratory, thoracic and mediastinal disorders	• Interstitial pneumonitis
	Hepatobiliary disorders	• Cirrhosis of the liver
Rare (≥ 0.01% and <0.1%)	Blood and lymphatic system disorders	• Neutropenia[a] • Agranulocytosis[a]
	Eye disorders	• Corneal changes • Optic neuropathy[a]

Table 2 Adverse Drug Reactions (ADR) seen with Tamoxifen Citrate*

Frequency	System Organ Class (SOC)	ADR
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	• Uterine Sarcoma (mostly malignant mixed Mullerian tumours)[a]
	Reproductive system and breast disorders	• Vaginal polyps[a] • Endometriosis[a] • Cystic ovarian swelling[a]
	Nervous system	• Optic neuritis
	Hepatobiliary disorders	• Hepatitis • Cholestasis[a] • Hepatic failure[a] • Hepatocellular injury[a] • Hepatic necrosis[a]
	Skin and subcutaneous tissue	• Angioedema • Steven-Johnson syndrome[a] • Cutaneous vasculitis[a] • Bullous pemphigoid[a] • Erythema multiforme[a] • Cutaneous lupus erythematosus[b]
	Congenital, familial and genetic disorders	• Porphyria cutanea tarda[b]

* 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 ≤ 0.1% from the ATAC study (A Randomized, Double-Blind Trial Comparing anastrozole to tamoxifen citrate).

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'.

Rare reports of erythema multiforme, Stevens-Johnson syndrome, cutaneous vasculitis, and bullous pemphigoid, and 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 WARNINGS AND PRECAUTIONS).

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 and, in a small number of cases, blindness has occurred.

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 (see WARNINGS AND PRECAUTIONS).

Liver abnormalities reported include 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).

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

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.

8.5 Post-Market Adverse Reactions

Cases of radiation recall have been reported in patients receiving tamoxifen citrate in the post-marketing setting. The reaction is usually reversible upon temporary cessation of therapy and re-challenge may result in a milder reaction. Treatment with tamoxifen citrate was continued in most cases.

Myalgia has been reported in patients receiving tamoxifen citrate in the post-market setting. In post-market reports, discontinuation of treatment resulted in resolution of symptoms.

9 DRUG INTERACTIONS

9.2 Overview

The known principal pathway for tamoxifen citrate metabolism in humans is demethylation, catalyzed by CYP3A4 enzymes. A pharmacokinetic interaction with the CYP3A4 inducing agent

rifampicin, involving a reduction in tamoxifen citrate plasma levels has been reported in the literature. The relevance of this to clinical practice is not known.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen citrate metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen), has been reported in the literature. Chronic use of CYP2D6 inhibitors can lead to reduced plasma concentrations of an active metabolite (see WARNINGS AND PRECAUTIONS).

9.4 Drug-Drug Interactions

TEVA-TAMOXIFEN 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 WARNINGS AND PRECAUTIONS).

The interactions listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

When tamoxifen citrate is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur (see WARNINGS AND PRECAUTIONS). Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

When tamoxifen citrate is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see WARNINGS AND PRECAUTIONS).

The use of tamoxifen citrate in combination with an aromatase inhibitor as adjuvant therapy has not shown improved efficacy compared with tamoxifen citrate alone. Coadministration of anastrozole and tamoxifen citrate in breast cancer patients reduced anastrozole plasma concentration by 27% compared to those achieved with anastrozole alone. However, clinical significance of this reduction is unknown.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 tumours. In this rat model, tamoxifen citrate appears to exert its antitumour effects by binding to estrogen receptors.

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

10.2 Pharmacodynamics

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 0-300 fmol/mg protein have been reported in histologically comparable portions of the same tumour. In addition, the collection, transport and storage of tumour 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.

10.3 Pharmacokinetics

Metabolism: Preliminary pharmacokinetics in women using radiolabeled tamoxifen citrate have shown that most of the radioactivity is slowly excreted in the feces, with only small amounts appearing in urine. The drug is excreted mainly as conjugates, with unchanged drug and hydroxylated metabolites accounting for 30% of the total. Blood levels of total radioactivity following single oral doses of approximately 0.3 mg/kg reached peak values of 0.06-0.14 mcg/mL at 3-7 hours after dosing, with only 20-30% of the drug present as tamoxifen citrate. There was an initial half-life of 7-14 hours with secondary peaks four or more days later. The prolongation of blood levels and fecal excretion is believed to be due to enterohepatic circulation.

11 STORAGE, STABILITY AND DISPOSAL

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

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

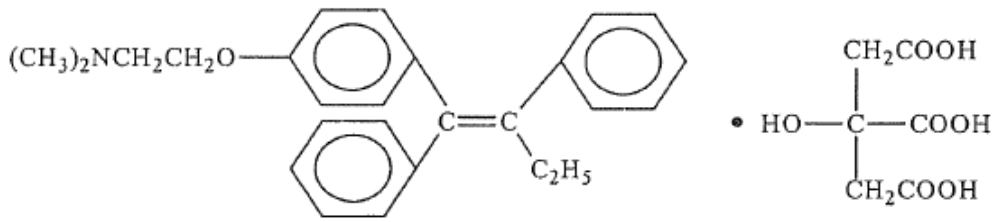
Drug Substance

Proper Name: Tamoxifen Citrate

Chemical Name: (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

Molecular Formula: $C_{26}H_{29}NO\ C_6H_8O_7$ Molecular Weight: 563.62 g/mol

Structural Formula:



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

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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The original data on which the indication was approved is not available.

14.2 Study Results

The original data on which the indication was approved is not available.

14.3 Comparative Bioavailability Studies

A two-way crossover, single dose, oral comparative bioavailability study of TEVA-TAMOXIFEN 20 mg tablets versus NOLVADEX®-D 20 mg tablets (Zeneca Pharma Inc.) was conducted in 10 healthy adult male volunteers. The results from the study are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Tamoxifen (1 x 20 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	2141.52 (35)	2243.28 (28)		
C_{max} (ng/mL)	32.67 (32)	32.99 (20)		
T_{max}[3] (h)	5.52 (8.7)	5.28 (13)		

[1] TEVA-TAMOXIFEN (tamoxifen citrate) tablets, 20 mg, Teva Canada Inc.
[2] NOLVADEX®-D (tamoxifen citrate) tablets, 20 mg, Zeneca Pharma Inc. (Canada)
[3] Expressed as the arithmetic mean (CV%) only.

In another study, a two-group parallel, single-dose, oral comparative bioavailability study of TEVA-TAMOXIFEN 20 mg tablets versus NOLVADEX®-D 20 mg tablets (Zeneca Pharma Inc.) was conducted in healthy adult male volunteers under fasted conditions. The results from 69 volunteers who completed the study are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Tamoxifen (1 x 20 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
$AUC_{0\text{-}72h}$ (ng·h/mL)	763.4 782.1 (22)	819.7 846.9 (27)	93.1	84.5 – 102.6

AUC_I (ng·h/mL)	2154.1 2251.0 (30)	2327.4 2458.9 (34)	93	
C_{max} (ng/mL)	27.31 28.10 (26)	29.48 30.36 (25)	92.7	84.1 – 102.1
T_{max}[3] (h)	5.2 (34)	5.0 (26)		
$t_{½}$[3] (h)	180.0 (27)	177.3 (30)		
[1] TEVA-TAMOXIFEN (tamoxifen citrate) tablets, 20 mg, Teva Canada Inc. [2] NOLVADEX®-D (tamoxifen citrate) tablets, 20 mg, Zeneca Pharma Inc. (Canada) [3] Expressed as the arithmetic mean (CV%) only.				

16 NON-CLINICAL TOXICOLOGY

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.

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 spermatocytes 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 citrate 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 citrate 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.

Antiestrogenic Effect

In those species in which tamoxifen citrate 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 that, 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 citrate 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.

17 SUPPORTING PRODUCT MONOGRAPH

1. NOLVADEX® - D Tablets, 20 mg, submission control # 243317, Product Monograph, AstraZeneca Canada Inc. MAR. 08, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEVA-TAMOXIFEN
Tamoxifen Citrate Tablets

Read this carefully before you start taking **TEVA-TAMOXIFEN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-TAMOXIFEN**.

Serious Warnings and Precautions

- TEVA-TAMOXIFEN was linked with serious and life-threatening events in a breast cancer prevention study. These included uterine cancer, stroke, blocked blood vessel in the lungs (pulmonary embolism), and blood clots forming in deep veins like the legs (deep vein thrombosis). These events were fatal in some patients. **TEVA-TAMOXIFEN is not approved for the prevention of breast cancer in Canada**.

- The benefit of TEVA-TAMOXIFEN outweighs the risks in most women who receive TEVA-TAMOXIFEN for the treatment of their breast cancer. In Canada, TEVA-TAMOXIFEN is approved for the treatment of breast cancer (see "What is TEVA-TAMOXIFEN used for?").

- Talk to your healthcare professional if you have any questions about your treatment with TEVA-TAMOXIFEN and any potential side effects.

What is TEVA-TAMOXIFEN used for?

TEVA-TAMOXIFEN is used in women to treat:

- Early-stage breast cancer after surgery, radiation or chemotherapy in patients with tumours that are estrogen receptor positive.
- Breast cancer that is called hormone responsive locally advanced or metastatic.

TEVA-TAMOXIFEN should only be used for the conditions listed above.

How does TEVA-TAMOXIFEN work?

TEVA-TAMOXIFEN blocks the effects of the hormone estrogen in your body.

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

What are the ingredients in TEVA-TAMOXIFEN?
Medicinal ingredients: tamoxifen citrate
Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, mannitol, magnesium stearate, povidone, polyethylene glycol, sodium starch glycolate and titanium dioxide.

TEVA-TAMOXIFEN comes in the following dosage forms:
Tablets 10 mg, 20 mg.

Do not use TEVA-TAMOXIFEN if you:

- Are allergic to tamoxifen citrate.
- Are allergic to any of the other ingredients in TEVA-TAMOXIFEN.
- Are allergic to any part of the TEVA-TAMOXIFEN container.
- Are pregnant.
- Are under 18 years of age.
- Have had a stroke in the past.
- Have had a pulmonary embolism in the past which is when a blood vessel in your lungs is blocked.
- Have had blood clots in the past, including deep vein thrombosis which is when blood clots form in deep veins like the legs.
- Are taking medicines called anticoagulants used to prevent blood clots, like warfarin.
- Have been told by your healthcare professional that you have an increased risk of developing cancer of the endometrium.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-TAMOXIFEN. Talk about any health conditions or problems you may have, including if you:

- Are breastfeeding or intend to breastfeed.
- Are taking or have recently taken antidepressant medicines such as paroxetine used to improve mood or symptoms of hot flushes.
- Have cataracts or other eye problems.
- Have decreased white blood cells or platelets in your blood.
- Are taking medicines called aromatase inhibitors used for endocrine therapy, such as anastrozole, letrozole or exemestane.
- Are taking medicines called cytotoxic agents used to destroy cancer cells.
- Have metastatic bone disease or elevated calcium levels (hypercalcemia).

Other warnings you should know about:

Pregnancy:

Tell your healthcare professional if you are planning to become pregnant or if you think you might have become pregnant. You must not take TEVA-TAMOXIFEN if you are pregnant. This is

because it may harm your unborn baby. You must use effective birth control while you are taking TEVA-TAMOXIFEN and for nine months after you stop taking it. Talk to your healthcare professional about effective methods of birth control.

Breast reconstruction surgery:

Tell your healthcare professional if you are planning to have breast reconstruction surgery called microvascular breast reconstruction. This is where your own tissue is used to make a new breast. It can occur weeks to years after your primary cancer surgery. Taking TEVA-TAMOXIFEN when you have microvascular breast reconstruction surgery can increase your risk of complications.

Endometrial and uterine cancer and fibroids:

Taking TEVA-TAMOXIFEN can increase your risk of getting endometrial or uterine cancer or uterine fibroids (non-cancerous tumours in your uterus). Tell your healthcare professional right away if you have any unusual vaginal bleeding or pelvic pain or pressure when you are taking TEVA-TAMOXIFEN or anytime afterwards. This is because a number of changes to the lining of the endometrium and uterus may occur, some of which may be serious and could include cancer.

If you go into the hospital, let medical staff know you are taking TEVA-TAMOXIFEN. **Driving and using machines:**

TEVA-TAMOXIFEN may make you tired and weak. This may affect your ability to drive and use machines. Before driving or using machines, wait until you are feeling well again.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TEVA-TAMOXIFEN:

- Take TEVA-TAMOXIFEN exactly as your healthcare professional tells you to.
- It is important to keep taking TEVA-TAMOXIFEN even if you start to feel ill. Do not change your dose or stop taking this medicine without talking to your healthcare professional.
- Stay under your healthcare professional's care while taking TEVA-TAMOXIFEN.

Usual dose:

The recommended daily dose of TEVA-TAMOXIFEN is 20 to 40 mg in a single dose or in two divided doses. The lowest effective dose should be used. Your healthcare professional will tell you how much TEVA-TAMOXIFEN to take and when to take it.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVA-TAMOXIFEN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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 make up for a missed dose.

What are possible side effects from using TEVA-TAMOXIFEN?

These are not all the possible side effects you may feel when taking TEVA-TAMOXIFEN. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Hot flushes
- Itching around the vagina
- Vaginal discharge
- Nausea, vomiting, diarrhea and constipation
- Bad taste in the mouth, loss of taste or distaste to food
- Headaches
- Light-headedness
- Sensory changes (including taste disorder and numbness or tingling in the skin)
- Hair loss
- Leg cramps
- Tingling, numbness or prickling of the skin
- Muscle pain
- Tiredness and weakness
- Disturbances of menstrual function, irregular or missed menstrual periods
- Depression
- Increased levels of fats in the blood, sometimes with pain or tenderness in the upper abdomen.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			

Fluid retention (excess fluid build-up inside the body): Swelling of the hands, feet or ankles.	√		
COMMON			
Anemia (decreased red blood cells): Dizziness, feeling tired and weak, loss of energy, shortness of breath.		√	
Cataracts (change to the cornea or disease of the retina): Disturbances of vision or difficulties in seeing properly.		√	
Endometrial changes (non-cancerous mass in the inner lining of the vagina): Vaginal bleeding, irregular periods with heavy bleeding.		√	
Fatty liver (formation of fatty liver cells): Fatigue, malaise, upper abdominal discomfort, general feeling of being unwell, with or without jaundice (yellowing of the skin and eyes).		√	
Hypersensitivity Reactions (allergic reactions): Develop 'nettle rash' or 'hives' (urticaria).			√
Ischemic cerebrovascular events (stroke): Numbness, paralysis or weakness of the arms or legs, dizziness or confusion, slurred/loss of speech, sudden difficulty walking, difficulty in holding things.			√
Liver test abnormalities (blood tests showing elevations in liver enzymes): Abdominal pain, nausea, vomiting, abdominal distension, with or without jaundice (yellowing of the skin and eyes).		√	
Radiation recall (inflammation of skin due to radiation): Redness, peeling, swelling, and/or blistering of the skin in areas previously exposed to radiation therapy.		√	
Thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism			√

(clot in blood vessels): Pain, swelling or redness of the calf or leg which may indicate a blood clot in the deep veins of leg. Chest pain or shortness of breath which may indicate a blood clot in lungs.			
Tumour Flare (inflammation of visible tumour): Increased bone and tumour pain.		√	
Uterine fibroids (non-cancerous tumours in your uterus): Vaginal bleeding, pelvic discomfort or irregular periods with heavy bleeding.		√	
UNCOMMOM			
Endometrial cancer (cancers of the inner lining of the endometrium): Vaginal bleeding, pelvic discomfort, irregular periods with heavy bleeding.		√	
Hypercalcemia (increased calcium levels in the blood): Excessive nausea, vomiting or thirst.		√	
Interstitial pneumonitis (inflammation of the lungs): Breathlessness and cough.		√	
Leukopenia (low white blood cell counts): Aches, feeling tired, fever, flu-like symptoms, infections.		√	
Liver cirrhosis (scarring of the liver): General feeling of being unwell, with or without jaundice (yellowing of the skin and eyes).		√	
Pancreatitis (inflammation of the pancreas): Prolonged severe abdominal pain with or without vomiting, pain may spread out towards the back, pain or tenderness in upper abdomen.		√	
Thrombocytopenia (decreased platelets in the blood): Bleeding, bruising, fatigue, weakness.		√	
Visual disturbances, including retinal crystals, macular edema, keratopathy (abnormal vision, red eye and damage to the retina of the eye): Change in eye colour, difficulty seeing		√	

at night or in poor light, eye pain, eye swelling and redness, watery eyes, vision changes, and sensitivity to light.			
RARE			
Agranulocytosis (decreased white blood cells) and Neutropenia (decreased counts of neutrophils): Aches, feeling tired, fever, flu-like symptoms, infections.		√	
Angioedema (swelling due to allergic reaction): Difficulty in breathing with or without swelling of the face, lips, tongue and/or throat and/or swelling of the face, lips, tongue and/or throat which may cause difficulty swallowing.			√
Bullous pemphigoid (large fluid-filled blisters on skin): Redness, itching of skin and/or blistering of the skin, lips, eyes or mouth.			√
Cutaneous lupus erythematosus (inflammation of the skin): Rash or redness on areas exposed to light.		√	
Cutaneous vasculitis (inflammation of the blood vessels): Red spots on skin that don't change colour when pressed, bruise-like marks on the skin, raised skin lumps.		√	
Endometriosis (abnormal growth of the uterus lining): Painful periods with excessive bleeding, pain on urination or pelvic discomfort/pain.		√	
Erythema multiforme (allergic skin reaction): Raised red or purple skin patches, possibly with blister or crust in the centre, possibly with mild itching or burning; possibly swollen lips.			√
Liver abnormalities, including cholestasis, hepatitis, hepatic failure, hepatocellular injury, hepatic necrosis (Liver Injury): General feeling of being unwell, with or without jaundice, nausea and		√	

vomiting (yellowing of the skin and eyes).			
Optic nerve diseases, including optic neuropathy, optic neuritis (damage to optic nerve): Blurred vision, blindness.		√	
Ovarian cysts (enlargement of the ovaries): Pressure, bloating, swelling or pain in the lower abdomen on the side of the cyst.		√	
Porphyria cutanea tarda (skin lesions): Skin blisters in areas exposed to the light.		√	
Steven-Johnson syndrome (severe skin reactions): Fever, redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands.			√
Uterine cancer (cancers of the uterus): Vaginal bleeding, pelvic discomfort, irregular periods with heavy bleeding.		√	
Vaginal polyps (non-cancerous mass in the inner lining of the vagina): Vaginal bleeding, irregular periods with heavy bleeding.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

- TEVA-TAMOXIFEN should be stored at room temperature (15 to 30°C) and protected from light.
- Keep out of reach and sight of children.

If you want more information about TEVA-TAMOXIFEN:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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