PRODUCT MONOGRAPH

TAMOFEN®
(Tamoxifen Citrate)

10 and 20 mg Tablets

Antineoplastic

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NAME OF DRUG

TAMOFEN®

tamoxifen citrate tablets 10 mg and 20 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic (non-steroidal antiestrogen)

TAMOXIFEN THERAPY WAS ASSOCIATED WITH SERIOUS AND LIFE-THREATENING EVENTS INCLUDING UTERINE MALIGNANCIES, STROKE, PULMONARY EMBOLISM, AND DEEP VEIN THROMBOSIS IN THE NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT (NSABP) P-1 BREAST CANCER PREVENTION TRIAL. THE USE OF TAMOXIFEN FOR BREAST CANCER PREVENTION IS NOT AN APPROVED INDICATION IN CANADA. THE FOLLOWING RISKS ASSOCIATED WITH TAMOXIFEN THERAPY HAVE BEEN ESTIMATED FROM THE NSABP P-1 BREAST CANCER PREVENTION TRIAL. THE RELATIVE RISK OF TAMOXIFEN 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 TAMOXIFEN THERAPY AND SHOULD DISCUSS THEM WITH THEIR PATIENTS.

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

ACTIONS AND CLINICAL PHARMACOLOGY

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

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

Reports of advanced breast cancer trials conducted world-wide, however, indicate that, using established criteria, there is an objective response rate (complete and partial remission) to tamoxifen of approximately 10% in patients with estrogen receptor negative tumors which may indicate other mechanisms of action. A further small percentage of patients show positive benefit in that they are reported to have disease stabilization. This may be explained by the shortcomings of the assay procedure or by actions of tamoxifen at loci other than the estrogen receptor.

Ranges as large as 0 - 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. See the TOXICOLOGY section for details of the ESTROGEN RECEPTOR ASSAY.

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 are mediated through the estrogen receptor. Tamoxifen 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 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 tumor growth.

It is recognized that tamoxifen also displays estrogenic-like effects on several body systems including the endometrium, bone and blood lipids.

INDICATIONS

TAMOFEN (tamoxifen citrate) is indicated for the adjuvant treatment of early breast cancer in women with estrogen receptor positive tumors. TAMOFEN is indicated for the treatment of women with hormone responsive locally advanced/metastatic breast cancer.

CONTRAINDICATIONS

When used in the prevention setting (an indication not approved in Canada), 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. Tamoxifen is not indicated for the prevention of breast cancer in Canada.

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. 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.

Women should be advised not to become pregnant while taking tamoxifen 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 appraised of the potential risks to the fetus, should they become pregnant while taking tamoxifen or within two months of cessation of therapy.

Tamoxifen is contraindicated in patients with hypersensitivity to tamoxifen or any of its components.

WARNINGS

An increased incidence of uterine malignancies has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen. Most uterine malignancies seen in association with tamoxifen are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed Mullerian 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 ($\geq$2 years) of tamoxifen than non-users.

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen therapy. When tamoxifen 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 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 therapy in high-risk patients being treated for the prevention of breast cancer. The use of tamoxifen for the prevention of breast cancer is not an approved indication in Canada.

Incidence rates for the above 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 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.

In rats, tamoxifen can induce preneoplastic and neoplastic changes of the liver including hepatocellular carcinomas when administered at high doses for prolonged periods. In that species tamoxifen behaves as a partial agonist whereas it is primarily an antiestrogen in humans. For this reason and considering the high dosage used in the rat studies (up to 100 times the normal human therapeutic dose), the relevance of these findings to human use in unknown.

Hepatocellular carcinomas have been reported in a 2 year oncogenicity study in rats receiving tamoxifen. In addition, gonadal tumors have been reported in mice receiving tamoxifen in long-term studies. 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 has been associated with an increased incidence of cataracts.

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.

TAMOFEN (tamoxifen citrate) should be used only for the conditions listed under the Indications section.

PRECAUTIONS

Use TAMOFEN (tamoxifen) cautiously in patients with existing thrombocytopenia or leukopenia. Transient decreases in platelet counts usually to 50,000-100,000/mm^3, have been observed occasionally during treatment. However, no hemorrhagic tendency was reported and platelet counts returned to normal even though treatment was continued.

Transient decreases in leukocytes also have been observed occasionally during treatment. Although it was uncertain that these incidences of leukopenia and thrombocytopenia were due to tamoxifen 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. Patient who have metastatic bone disease should have periodic serum calcium determinations during the first few weeks of TAMOFEN therapy and any symptoms suggestive of hypercalcemia should be evaluated promptly. If hypercalcemia is present, appropriate measures should be taken, and, if severe, TAMOFEN 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. If adverse reactions such as hot flushes, nausea or vomiting occur, and are severe, they may be controlled in some patients by a dosage reduction without loss of effect on the disease.

Bone pain, if it should occur, may require analgesics.

Any patients receiving tamoxifen or having previously received tamoxifen who report abnormal 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 25% of patients who eventually responded were treated for four or more months before a definite objective response was recorded.

The duration of TAMOFEN treatment will depend on the patient's response. The drug should be continued as long as there is a favourable response.

With obvious disease progression, discontinue TAMOFEN. 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 TAMOFEN, 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 Interaction: When tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring.

ADVERSE REACTIONS

The most frequent adverse reactions to TAMOFEN (tamoxifen) are hot flushes, nausea and vomiting. These may occur in up to 25% of patients and are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding and vaginal discharge. Any patients reporting these symptoms should be promptly investigated. An increased incidence of uterine cancer and uterine sarcomas has been reported in association with tamoxifen treatment (see WARNINGS).

Skin rashes, have also been reported. Usually these have not been severe enough to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and also local disease flare have occurred. These are sometimes associated with good tumor 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 TAMOFEN and generally subside rapidly.

Ocular changes have been reported in a few breast cancer patients who, as part of a clinical trial, were treated for periods longer than one year with doses of tamoxifen that were at least four times the highest recommended daily dose of 40 mg. In each instance, the total amount of drug exceeded 100 grams. These changes were a retinopathy and, in a few patients, corneal changes and decreased visual acuity. There were multiple light refractile opacities in the paramacular area, and macular edema. The corneal lesions consist of whorl-like superficial opacities.

A number of cases of visual disturbances, including infrequent reports of corneal changes, and retinopathy have been described in patients receiving tamoxifen therapy. An increased incidence of cataracts has been reported in association with the administration of tamoxifen.

Leukopenia has been observed following the administration of tamoxifen, sometimes in association with anemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe.

Elevations of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and gamma-glutamyl transpeptidase (GT) levels have been reported on rare occasions in association with tamoxifen therapy. The incidence of overt cholestasis appears to be very low (<1%) but it should be kept in mind while administering tamoxifen over the long term.

There have been infrequent reports of thromboembolic events occurring during tamoxifen citrate therapy. As an increased incidence of these events is known to occur in patients with malignant disease, a causal relationship with tamoxifen citrate has not been established.

Other adverse reactions noted infrequently are hypercalcemia, peripheral edema, benign symptomatic hepatic cysts, peliosis hepatitis, distaste for food, pruritus vulvae, depression, dizziness, light headedness and headache.

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported. Ovarian cysts have been observed in a small number of pre-menopausal patients with advanced breast cancer who have been treated with tamoxifen.

Importantly, increased incidence of uterine malignancies, including endometrial adenocarcinomas and uterine sarcomas, have been reported in association with tamoxifen therapy (see WARNINGS).

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Acute overdosage in humans has not been reported. Possible overdosage effects might include hot flushes, nausea, vomiting and vaginal bleeding.

Treatment: Symptomatic treatment. In the case of childhood accidental ingestion, gastric emptying is suggested.

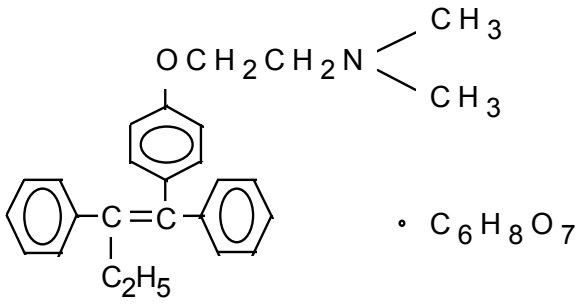
DOSAGE AND ADMINISTRATION

The usual dose is 20 to 40 mg per day in a single or two divided doses. Use the lowest effective dose.

In early disease, the recommended duration of therapy is 5 years. The optimal duration of therapy remains to be determined.

PHARMACEUTICAL INFORMATION

Tamoxifen citrate is the trans-isomer of (Z)-2-[p-(1,2-Diphenyl-1 butenyl) phenoxy]-N, N-dimethylethylamine citrate (1:1).



Molecular formula: $C_{26}H_{29}NO.\ C_6H_8O_7$

Molecular weight: 563.65

Description:
Tamoxifen citrate is a fine white, odourless crystalline powder. It is soluble in methanol, sparingly soluble in ethanol and acetone, and very slightly soluble in water. It is hygroscopic and photosensitive.

Melting point: About 142°C.

Stability and Storage recommendations:
Store at room temperature (between 15 and 30°C) in a well closed container. Protect from light.

DOSAGE FORMS

TAMOFEN (tamoxifen citrate) 10 mg tablets - white, round, biconvex tablets, marked T/10 on one side and scored on the other; contains 15.2 mg tamoxifen citrate equivalent to 10 mg of tamoxifen base. Non-Medicinal ingredients: lactose monohydrate, maize starch, silica colloidal anhydrous, povidone, talc, magnesium stearate and purified water. Plastic containers of 60 and 250 tablets; or boxes of 60 tablets in aluminium film strips (unit dose packages).

TAMOFEN (tamoxifen citrate) 20 mg tablets - white round, biconvex tablets, marked T/20 on one side; contains 30.4 mg tamoxifen citrate equivalent to 20 mg tamoxifen base. Non-Medicinal ingredients: lactose monohydrate, maize starch, silica colloidal anhydrous, povidone, talc, magnesium stearate and purified water. Plastic containers of 60 tablets; or boxes of 30 and 60 tablets in aluminium film strips (unit dose packages).

INFORMATION FOR THE PATIENT

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.

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 TAMOFEN Contain).
- 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).
- 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 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 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 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 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 any other prescription 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 go into the hospital, let medical staff know you are taking tamoxifen.

Who Should Not Take TAMOFEN
- If you have ever had any unusual or allergic reaction to tamoxifen or any one of its ingredients (See What Does TAMOFEN Contain).
- If you are pregnant or if you intend to become pregnant.

Proper Use of This Medication
Use this medication 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.

What Does TAMOFEN Contain
The medicinal ingredient of TAMOFEN is the tamoxifen citrate. Each tablet of TAMOFEN also contains the following non-medicinal ingredients: lactose monohydrate, maize starch, silica colloidal anhydrous, povidone, talc, magnesium stearate and purified water.

To Store this Medicine:
- KEEP OUT OF THE REACH OF CHILDREN.
- Store away from heat and 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.

Side Effects of This Medicine
Along with its needed effects, 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 chance of cancer of the uterus (womb) as well as fibroids (non-cancerous tumors) in the uterus in some women taking it. It may also cause a drop in some of your blood cell counts. In addition, tamoxifen 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 undesirable events occur:

Do not be alarmed by this list of possible events. You may not have any of them.
- Hot flushes
- Menstrual disturbances
- Effects on the endometrium (lining of the womb), which may also be seen as vaginal bleeding
- Fibroids (causes enlargement of the womb), which may also be seen as discomfort in the pelvis or as vaginal bleeding
- Itching around the vagina
- Vaginal discharge
- Stomach upsets (including nausea and vomiting)
- Light-headedness
- Fluid retention (possibly seen as swollen ankles)
- Bruising more easily (thrombocytopenia)
- Skin rash
- Hair loss
- Certain liver problems such as jaundice (yellow eyes)
- Disturbances of vision

- Difficulties in seeing properly possibly due to cataracts, changes to the cornea or disease of the retina
- Ovarian cysts (fluid sacs on ovaries) in premenopausal women
- Increased risk of blood clots
- 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
- Symptoms of stroke, such as weakness, difficulty walking or talking, or numbness
- 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.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

If you need further information ask your doctor or pharmacist.

PHARMACOLOGY

Pharmacodynamics

In animal species tamoxifen usually acts as an anti-estrogen compound inhibiting the effects of exogenous estrogen probably by binding with cytoplasmic estrogen receptors with subsequent translocation into the nucleus but without producing typical estrogen response. In rodents however it can also induce atypical or weak estrogenic effects.

In those species in which 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 and in immature rats the uterotrophic effect of estrogen can be similarly inhibited.

Also in rats, tamoxifen 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 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 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 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 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 given at the same time.

Although the capacity of tamoxifen (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 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.

Tamoxifen has been shown to inhibit or reverse the growth of some dimethylbenzathracene (DMBA)-induced carcinomas in rats and to decrease the frequency of tumor development when administered concurrently with DMBA. The responsiveness of DMBA-induced tumors was correlated with their estrogen-binding capacity.

In studies using estrogen-dependent human cancer cell cultures tamoxifen inhibited cell production, as determined by measuring the rate of incorporation of radiolabelled thymidine into macromolecules. The simultaneous addition of estrogen to tumor cultures along with tamoxifen either prevented or reversed tamoxifen's inhibitory effect. However, incubation of tumor cells with tamoxifen alone for longer that 3 days produced irreversible inhibition of growth.

Pharmacokinetics and Metabolism

The absorption, distribution and excretion of tamoxifen have been studied with radio-labelled tamoxifen. After a single dose of 20 mg of tamoxifen maximum blood levels occurred at 4 to 7 hours after drug administration whereby 20% to 30% of the original radioactivity were found in plasma. Radioactivity in the uterus was about twice that in the serum. The highest concentration occurred in the endometrium. The distribution half-life was about 7 to 14 hours after single dose. However after continued administration it was greatly prolonged (7 days).

The elimination of tamoxifen is biphasic. A considerable enterohepatic circulation has been demonstrated which probably is the reason for the slow elimination. Tamoxifen is mainly excreted in the feces with only small amounts appearing in the urine. Tamoxifen is primarily excreted as conjugates with unchanged drug and hydroxylated metabolites accounting for 30% of the total.

The two major metabolites are 4-hydroxytamoxifen and desmethyltamoxifen. Both possess antiestrogenic activity.

Bioavailability

A cross-over bioavailability study has also been carried out in which RHÔNE-POULENC's brand TAMOFEN was compared to NOLVADEX (ICI): thirty-two healthy males volunteers took part in the study; each subject received a single oral dose of 2 x 10 mg tablets of tamoxifen. A drug-free interval of 70 days was allowed between the administration of the two brands.

Following drug administration, plasma concentrations of tamoxifen were determined over a 21-day period by H.P.L.C. The mean comparative pharmacokinetic parameters of the two brands of tamoxifen tablets are presented in the following table.

Mean pharmacokinetic parameters of tamoxifen (± SEM)
(32 subjects: single dose; 2 x 10 mg tablets)

Brand	Cmax (ng/mL)	Tmax (h)	T½ (h)	AUC (h.ng.mL-1)	Relative Bioavailability
Tamofen	38.2 ± 1.30	4.4 ± 0.20*	109.3 ± 8.85	2338.9 ± 118.57	99.2 ± 5.36 %
Nolvadex	37.6 ± 1.58	5.1 ± 0.30*	112.3 ± 7.44	2474.1 ±136.89	

*significantly different $p < 0.05$

A significant difference between brands was detected for Tmax values. Considering the pharmacokinetic properties of tamoxifen, this difference has no clinical significance.

The power of the study to detect a 20% difference between TAMOFEN and NOLVADEX was greater than 0.99 for Cmax and greater than 0.93 for AUC .

The steady-state relative bioavailability of TAMOFEN was determined in 16 patients with advanced breast carcinoma in a randomized, multiple-dosing, cross-over study. Each patient received tamoxifen 20 mg daily as TAMOFEN or NOLVADEX for a period of 8 weeks at which point the medications were cross-over for another 8 weeks of treatment. At the end of each medication period, plasma samples were collected over one dosing interval. Plasma concentrations of tamoxifen (T), N-desmethyltamoxifen (DMT), N,N-didesmethyltamoxifen (DDMT) and metabolite Y were determined by HPLC. The corresponding AUC's were as follows:

Mean AUC values of tamoxifen and metabolites (± SEM) (h.ng.mL^{-1})

Brand	Tamoxifen	DMT	DDMT	Y
Tamofen	2987 ± 301.5	5345 ± 435.3	1148 ±119.3	890 ± 108.8
Nolvadex	2904 ± 265.3	5211 ± 363.8	1165 ± 104.3	859 ± 92.3

No significant difference was observed in the availability of any of tamoxifen or any of its metabolites.

TOXICOLOGY

Acute toxicity studies

The following table summarizes the main findings of the acute toxicity studies carried out with tamoxifen in mice and rats:

Species	Number of animals per group	Dosage and route of administration	LD50 (mg/kg)	Symptomatology
Mice	--	p.o.	3900	--
Mice	--	i.p.	270	--
Mice	5/sex/dose	i.v.	153	Convulsions
Rats	10/female/dose	p.o.	750*	Convulsions

*14 days

Long-term toxicity studies

Sub-acute and chronic toxicity studies have been carried out in mice, rats, dogs and monkeys with daily oral doses of tamoxifen. The following table summarizes the pertinent findings of these studies.

Species	Dosage and route	Duration	Observations & Findings
Rats	Oral 2, 20, 100 mg/kg	3 months	Effects primarily on the reproductive system.
Dogs	Oral up to 75 mg/kg	3 months	Effects primarily on the reproductive system. Biliary stasis also seen at the highest dose
Mice	Oral 0.1 to 50 mg/kg	14-15 months	Testicular and ovarian tumors and bone changes
Rats 12/sex/dose	Oral 100 mg/kg	29 days	All females and 3 males died within the first 2 weeks. Toxic symptoms included bleeding from nose, pilo-erection and weakness. Slight leukopenia, thrombo-cytopenia and anemia in male rats. At autopsy enlargement of adrenals and smaller thymus and seminal vesicles.
Rats 12/sex/dose	Oral 35, 70 mg/kg	3 months	50% of females and 17% of males died at both dose levels. Food intake increased, nose bleeding and decreased locomotor activity. At autopsy there was an increase in adrenal size and decrease in genital size. Histopathology showed atrophy of reproductive system and hyperplasia of adrenal cortex. Slight anemia and thrombo-cytopenia were also noted.
Rats 25/sex/dose	Oral 0.6, 6, 60 mg/kg	6 months (followed by 7-week recovery period)	At high dose: death of 40% of males and 20% of females; evidence of preneoplastic and/or neoplastic liver lesions. Other toxic symptoms included; severe decrease in body weights, loss of hair, cataracts in 12% of animals at high dose, atrophic changes of reproductive organs and increase in adrenal weights.
Rats 10/sex/dose	Oral 0.007, 0.7, 35 mg/kg	6 months	At intermediate and high dose: severe atrophic changes of reproductive organs. At high dose: slight anemia, leukopenia and thrombocytopenia; nodular hyperplasia of hepatocytes.
Monkeys (Callitrix jacchus) 2/sex/dose	Oral 5, 15, 45 mg/kg (70 mg/kg x 2 days but badly tolerated)	6 months (followed by 5-week recovery period)	One death at 70 mg/kg. At histopathology (in one or more animals): altera-tion of digestive mucosa, atrophy of splenic corpus-cules, and thymic cortex, calcification of myocardial cells, tubular cell necro-sis, minor alterations of spermatogenesis.

Mutagenicity studies

Four separate mutagenicity studies have been carried out with Tamoxifen. The following table summarizes the results of these investigations.

Test	Strains or Species	Drug/Dosage	Results
"Mohn" test	E. coli	Tamoxifen citrate 0.05, 0.15, 0.50, 1.50, 5.0 mg/mL	Tamoxifen citrate showed no increase in mutant colonies, but strong toxicity at 5.0 mg/mL and moderate toxicity at 1.5 mg/mL. Positive controls were
Micronucleus test	Mice	Tamoxifen citrate 5, 20 and 80 mg/kg. Negative control group (sodium citrate). Positive control group (cyclophosphamide)	Tamoxifen citrate showed a significant increase in polychro-matic erythrocytes at all dose levels in comparison to the negative control group but signifi-cantly less than the positive control group.
"Ames" test	Salmonella Typhimurium strains TA1538, TA1537, TA1539, TA100 and TA98	Tamoxifen 0, 1, 10, 100, 1000 /plate	No evidence of mutagenic activity of tamoxifen was ob-served either in the presence or absence of liver microsomal supplement.
Sister chromatid exchange test	Embryonal lung fibroblast (FH 109 line)	Tamoxifen citrate 0.25, 0.5, 1.0, 2.0, 4.0 g/mL	No significant in-crease in mean number of sister chromatid exchanges/ 46 chromosomes.
	Human lymphocytes	Same	Positive at concen-trations of 1 g/mL and above.

Tamoxifen is not mutagenic in a range of *in vitro* and *in vivo* mutagenicity studies. Tamoxifen was genotoxic in some *in vitro* tests and *in vivo* genotoxicity tests in rodents.

ESTROGEN RECEPTOR ASSAY

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 cells. 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 nonspecific 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 nonspecific 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 8 S complex, whereas others show various amounts of specific binding in the 4 S region as well. Radioactivity associated with the 8 S 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 4 S radioactivation 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 patient's response 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.

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