PRODUCT MONOGRAPH

[Pr]Dom-TAMOXIFEN

(Tamoxifen Citrate Tablets, USP)

10 mg & 20 mg

Antineoplastic Agent

DOMINION PHARMACAL
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PRODUCT MONOGRAPH

[Pr]Dom-TAMOXIFEN

(Tamoxifen Citrate Tablets USP)

10 mg & 20 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

TAMOXIFEN THERAPY WAS ASSOCIATED WITH SERIOUS AND LIFE-THREATENING EVENTS INCLUDING UTERINE MALIGNANCIES, STROKE, PULMONARY EMBOLISM, AND DEEP VEIN THROMBOSIS IN THE 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 ENDOMETRAIL 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.

ACTION AND CLINICAL PHARMACOLOGY

Tamoxifen citrate 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 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 worldwide, 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. A further small percentage of patients show positive benefit in that they are reported to fall into the disease stabilization category. 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 to 300 fmol/mg protein have been reported in histologically comparable portions of the same tumor. In addition, the collection, transport and storage of tumor specimens can affect the validity of current estrogen receptor assays (see section on 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.

Six studies (four single dose and two multiple dose studies) were conducted to compare Dom-TAMOXIFEN tablets to the reference Nolvadex tablets. The following is a summary of the studies which involved a crossover design (the rest were of parallel design):

A comparative single dose bioavailability study was carried out in which Dom-TAMOXIFEN was compared to Nolvadex (ICI Pharma) in 12 healthy male volunteers using a crossover design. The volunteers (after fasting) were randomized to treatment groups receiving either Dom-TAMOXIFEN 40mg (4 x 10mg tablets) or Nolvadex 40mg (4 x 10mg tablets). They were crossed over to the opposite medication after a wash-out period of 140 days. Blood samples were drawn just prior to dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 and 34 hours post-dose. Blood samples were assayed using a validated modification of the fluorimetric HPLC method of Golander and Stemson.

The mean comparative pharmacokinetic parameters of the two brands of tamoxifen tablets are represented in the following table:

	Dose (mg)	**C_{max} (ng/mL)**	**T_{max} (hours)**	**AUC (0-34) (ng-hrs/mL)**	**Relative Bioavailability**
Dom-TAMOXIFEN	4 x 10	62 ± 11	3.5 ± 1.0	978 ± 202	89%
Nolvadex	4 x 10	65 ± 22	3.8 ± 1.8	1099 ± 295	--

In an additional 12-week clinical study, twelve patients (fed state) were randomly allocated to treatment with either Dom-TAMOXIFEN tablets (3 x 10mg) daily or Nolvadex tablets (3 x 10mg) daily. The same lots of both preparations as in the previous study were used.
All patients were already receiving tamoxifen therapy for at least three months, at entry, and steady-state levels had been achieved.

After two weeks, patients were crossed over to the opposite treatment group. A second crossover took place after two more weeks (week 4), and a third and final switch was effected after another

two-week period (week 6). Trough blood samples were drawn pre-study and after 1, 2, 3, 4, 5, 6, 7, 8, and 12 weeks. Since patients were to be continuously maintained on their drug regimen, there was no wash-out period. The same HPLC assay as previously described was used. Average trough steady-state levels (C^{SS}) were computed from the results and are presented below:

Week	**Dom-TAMOXIFEN (Mean ± SD)**	**Nolvadex (Mean ± SD)**
1	122.5 ± 52.2	113.8 ± 53.6
2	122.9 ± 50.4	118.5 ± 30.7
3	112.1 ± 47.9	124.5 ± 38.4
4	129.5 ± 65.2	119.4 ± 55.1
5	118.7 ± 67.4	116.6 ± 34.9
6	152.8 ± 60.0	141.7 ± 78.5
7	134.5 ± 39.3	151.3 ± 70.2
8	167.5 ± 80.3	141.2 ± 71.6
12	136.9 ± 49.7	124.0 ± 45.9

Week 1 - 4, 13 patients Week 5 - 12, 12 patients

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Contraindicated in patients with hypersensitivity to tamoxifen.

When used in the prevention setting, 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.

Pregnancy: Tamoxifen must not be given during pregnancy. Premenopausal patients must be carefully examined before treatment to exclude the possibility of 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 1 000 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 to not 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.

WARNINGS

Tamoxifen should be used only for the conditions listed under **INDICATIONS**.

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 of 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.

Disturbances of menstrual function, including oligomenorrhea and amenorrhea, have been reported in a proportion of premenopausal women receiving tamoxifen for the treatment of breast cancer. Available information indicates that in those women receiving tamoxifen for up to 2 years for the treatment of early breast cancer who develop disturbances of menstrual function on treatment, a proportion returned to normal cyclical bleeding on cessation of therapy.

Hepatocellular carcinomas have been reported in the 2-year oncogenicity study in rats receiving tamoxifen (see **TOXICOLOGY**). In addition, gonadal tumors have been reported in mice receiving tamoxifen in long-term studies (see **TOXICOLOGY**). The clinical relevance of these 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.

PRECAUTIONS

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

Transient decreases in leukocytes also have been observed occasionally during treatment. Although it was uncertain if these occasional incidences of leukopenia and thrombocytopenia were due to tamoxifen 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. Patients who have metastatic bone disease should have periodic serum calcium determinations during the first few weeks of tamoxifen therapy and any symptoms suggestive of of hypercalcemia should be evaluated promptly. If hypercalcemia is present, appropriate measures should be taken and, if severe, tamoxifen should be discontinued.

The first patient follow-up should be done within 1 month following initiation of treatment. Thereafter, examinations may be performed at 1- to 2- month intervals. If adverse reactions, such as hot flashes, 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.

Isolated cases of endometrial hyperplasia, endometrial polyps, and endometrial carcinoma have been reported with tamoxifen treatment. A definitive relationship to tamoxifen therapy has not been established. Women receiving tamoxifen or having previously received tamoxifen who report abnormal vaginal bleeding should be promptly investigated. Ovarian cysts have been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen.

In clinical studies, the median duration of treatment before the onset of a definite objective response has been 2 months. However, approximately 25% of patients who eventually responded were treated for 4 or more months before a definite objective response was recorded.

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

With obvious disease progression, discontinue tamoxifen. However, because an occasional patient will have a local disease flare (see **ADVERSE REACTIONS**), or an increase in bone pain shortly after starting tamoxifen, 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. Existing data suggest that, if possible, treatment should not be discontinued before a minimum of 3 to 4 weeks.

Drug Interactions: When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

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

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

ADVERSE REACTIONS

The most frequent adverse reactions to tamoxifen are hot flashes, nausea and vomiting. These may occur in up to 25% of all 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 sarcoma has been reported in association with tamoxifen treatment (see WARNINGS and PRECAUTIONS).

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

Other adverse reactions noted infrequently are hypercalcemia, peripheral edema, distaste for food, pruritus vulvae, depression, dizziness, lightheadedness, headache and alopecia.

If the above side effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dose range) without loss of control of the disease.

Skin rashes (including isolated cases of erythema multiforme, Stevens-Johnson syndrom and bullous pemphigoid), and rare hypersensitivity reactions, including angioedema have also been reported.

Ocular changes have been reported in a few breast cancer patients,who as part of a clinical trial, were treated for periods longer than 1 year with doses of tamoxifen that were at least 4 times the highest recommended daily dose of 40 mg. In each instance, the total amount of drug exceeded 100 g. 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.

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

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.

In the prevention section, treatment with tamoxifen has been associated with an increased risk of stroke (see WARNINGS). There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism during tamoxifen therapy.

Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen.

Elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gammaglutamyl transpeptidase (GGT) levels have been reported infrequently during tamoxifen citrated therapy. Overt cholestasis has occurred less frequently and, in addition, there have been rare reports of benign, symptomatic hepatic cyst and peliosis hepatitis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

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 in 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 a history of blood clots, including deep vein thrombosis (a blood clot in one 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 have ever had any unusual or allergic reaction to tamoxifen.
- If you are pregnant or 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 or other gynecological symptoms (such as pelvic pain or pressure) when you are taking tamoxifen or anytime afterwards. This is because a number of changes to the lining of the womb (the endometrium) may occur, some of which may be serious and could include cancer.
- If you are breastfeeding or intend to breastfeed.

- If you are taking 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 to the hospital, let medical staff know you are taking tamoxifen.

Proper Use of This Medicine:

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 chances of side effect, while taking too little may not improve your condition.

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

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

To store this medicine:

- **KEEP OUT OF THE REACH OF CHILDREN**
- **Store 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 improtant 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)
- Headaches
- Light-headedness
- Fluid retention (possibly seen as swollen ankles)
- Bruising more easily (thrombocytopenia)
- Increased levels of fats in the blood (hypertriglyceridemia) sometimes with pain or tenderness in your upper abdomen (pancreatitis)
- Skin rash or itching or peeling skin
- 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
- 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.
- 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

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

STOP TAKING TAMOXIFEN and contact your doctor immediately in any of the following situations:

- If you develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.
- If you develop swelling of the face,lips, tongue and/or throat which may cause difficulty swallowing.

If you need further information ask your doctor or pharmacist.

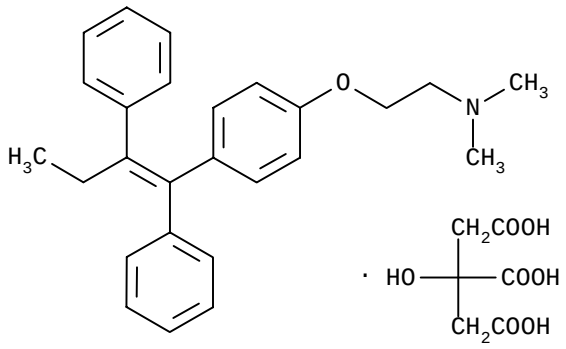
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Tamoxifen Citrate

Chemical Name:
1) Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N,N-dimethyl, (Z)-,2-hydroxy-1,2,3-propanetricarboxylate (1:1);
2) (Z)-2-[p-(1,2-diphenyl-1-butenyl) phenoxy]-N,N-dimethylethylamine citrate (1:1)

Structural Formula:



Molecular Formula: $C_{26}H_{29}NOC_6H_8O_7$

Molecular Weight: 563.65

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

Melting Range: Between 142˚ and 144.5˚C.

DOSAGE AND ADMINISTRATION

The recommended daily dose of 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.

AVAILABILITY OF DOSAGE FORMS

Dom-TAMOXIFEN (tamoxifen citrate) tablets 10 mg are white, round, scored, biconvex tablets and contain 15.2 mg tamoxifen citrate, equivalent to 10 mg of tamoxifen base. Available in PVC bottles of 100 and 250 tablets. Non-medicinal ingredients: Potato starch, lactose, Povidone K 25, Microcrystalline Cellulose, Magnesium Stearate, and Silicon Oxide.

Dom-TAMOXIFEN (tamoxifen citrate) tablets 20 mg are white, round, scored, biconvex tablets and contain 30.4 mg tamoxifen citrate equivalent to 20 mg of tamoxifen base. Available in PVC bottles of 100 tablets. Non-medicinal ingredients: Potato starch, lactose, Povidone K 25, Microcrystalline Cellulose, Magnesium Stearate, and Silicon Oxide.

Store at room temperature (15˚ to 30˚C) in a well-closed container. Protect from heat and light. .

PHARMACOLOGY

Pharmacokinetics and Metabolism:

Preliminary pharmacokinetics in womne using radiolabelled tamoxifen 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 µg/mL at 3 - 7 hours after dosing, with only 20 - 30% of the drug present as tamoxifen. There was an inital 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.

Antiestrogenic Effects:

In animal species tamoxifen usually acts as an antiestrogen compound inhibiting the effects of exogenous estrogen. It probably binds with cytoplasmic estrogen receptors, with subsequent translocation into the nucleus but without producing typical estrogen response. In rodents, however, it can also induct 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 blastocytes. 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 counter-acting 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 dimethylbenzanthracene (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 than 3 days produced irreversible inhibition of growth.

TOXICOLOGY

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

Three-month toxicity studies were conducted in rats and dogs. 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 absemce 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 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 liver 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.

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. 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.

In a 6-month rat study tamoxifen was administered orally at doses of 0.05 mg, 0.8 mg, 2.4 mg, 4.8 mg, and 9.6 mg/kg. Changes produced by tamoxifen were observed mainly in rats treated with 2.4, 4.8, and 9.6 mg/kg.

The reproductive organs showed severe atrophic changes increasing with dose from 2.4 to 9.6 mg/kg. Serum alkaline phosphatase and sodium levels were raised and alanine aminotransferase, aspartate aminotransferase and albumin levels were lowered. No significant histological findings were observed in the liver.

Chronic dosing in the marmoset involved one 6 month study. Tamoxifen 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 cycstically enlarged follicles in the ovaries of the females treated at 8.0 mg/kg.

The studies comparing tamoxifen with conventional estrogens showed the estrogenic activity of tamoxifen in mice was responsible for gonadal tumors. 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 with stilbestrol and ethinyl estradiol. Interestitial cell tumors of the testes and granulosa cell tumors 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 caesarean 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%.

Teratogenicity studies were conducted in rats and rabbits. Since tamoxifen 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 wwhich, 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 is not mutagenic in a range of *in vitro* and *in vivo* mutagenicity studies. Tamoxifen is not mutogenic 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 cell. Once bound to the chromatin, the interaction of the estrogen receptor complex with the genetic information of the cell leads to the elaboration of new species of messenger RNA. These molecules are then released into the cytoplasm where they can be translated on polysomes into new proteins.

Antiestrogens are also able to enter the cytoplasm of the estrogen-dependent cell and bind biologically to the protein receptor with affinity and specificity, thus activating the complex to also translocate to the nucleus. However, the normal estrogen transcriptional processes are altered. Hence, antiestrogens interfere with estrogen-dependent tumor growth by competing with estrogens for the receptor site and by turning off the normal processes of the genetic information within the nucleus.

Reports concerning the relationship between clinical responses of patients with breast cancer receiving endocrine therapy and the presence or absence of estrogen receptors have been compiled.

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

Methods:

a. Dextran-Coated Charcoal Assay (DCC)

The Dextran-Coated Charcoal assay (DCC) involves the extraction of the highly labile estradiol receptor from a cytosol prepared from the tumor tissue. After incubating with tritiated estradiol, which interacts with the binding sites of receptors, the excess estradiol

is separated from the incubate with dextran-coated charcoal. The amount of non-specific binding (e.g., albumin) is then determined and the quantity of estradiol receptors in the tissue is estimated from the difference in the total binding less non-specific binding per milligram of protein. Tumors which show binding capacity similar to benign tumors are designated ER-negative, while those with higher binding capacity are designated ER-positive.

b. Sucrose Gradient Method (SG)

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

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

<u>Interpretation of Results</u>:

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 of retrospective correlation made by various investigators based upon patient's response to hormonal manipulation, a result of less than 3 fmol/mg cytosol protein is considered ER-negative; 3 to 10 fmol/mg cytosol protein is

equivocal and over 10 fmol/mg is considered ER-positive.

ESTROGEN RECEPTOR MONOCLONAL ANTIBODIES

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

Most recently monoclonal antibody technology has been used to genreate a number of monoclonal antibodies specific for antigenic determinants on or near the estrogen receptor site. A number of antibodies have been produced by Greene and Jensen at the Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois. These specific monoclonal antibodies recognize the extranuclear estrogen receptor of the MCF-7 human breast cancer cell line. These antibodies bind to nuclear and cytosolic estrogen receptors from a variety of tissues and are therefore unique and specific probes for examining the structure and function of the estrogen receptor. Three such antibodies (D58, D75, D547) have been described to recognize different antigenic determinants on the receptor molecule. A combination of two such antibodies can be used in a sandwich technique for the immunoradiometric (IRMA) or enzyme-linked immunosorbent (EILSA) determination of estrogen receptor. These three antibodies recognize estrogen receptors in human breast cancer specimens as well as estrogen receptor in uterine tissue from other species. Further studies with the D547 and D58 monoclonal antibodies have revealed that these antibodies can distinguish among various forms of the estradiol-estrogen receptor complex. The antigenic determinants recognized by these particular antibodies on

breast tumor cytosolic receptors are not significantly altered by the binding of either estrogen or antiestrogen to the receptor. Studies such as this are able to demonstrate fundamental differences in the subcellular fate of the estrogen or antiestrogen-receptor complexes, and provide clues to the mechanism of action of estrogens and antiestrogens.

Poulsen has used two monoclonal antibodies specific for MCF-7 estrogen receptor to stain human breast cancer tissue sections using an immunoperoxidase technique. The immunoperoxidase staining was predominantly located in the nucleus of the malignant epithelial cells. No relationship between tumor type or degree of differentiation of invasive ductal carcinomas and staining features was observed. Poulsen found a significant positive correlation between the number of positively stained cells and cytosol receptor content. Similarly, King has developed monoclonal antibody D-5, an IgG_1, which binds to soluble estrogen receptor in a dose-dependent manner. Antibody D-5 is specific for human soluble estrogen receptor and will not react with other steroid-binding proteins or nuclear estrogen receptor. King found a highly significant correlation between estrogen receptor content and D-5 reactivity in human breast cancer sections. Kodama has used similar techniques to study the expression of estrogen receptors of human breast cancer clonal growth using the soft-agar cloning assay. He found that estrogen receptor expression increased with clonal growth of tumor cells to colonies and that estrogen receptor appeared to be expressed in the differentiation process. Finally, Edwards has developed a monoclonal antibody to the chicken oviduct progesterone receptor. This antibody also recognizes denatured human progesterone receptor as its antigen. Further applications of this monoclonal antibody are currently being examined.

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

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