PACKAGE INSERT TEMPLATE FOR TAMOXIFEN TABLET

Brand or Product Name
[Product name] Tablet 10mg
[Product name] Tablet 20mg

Name and Strength of Active Substance(s)

Tamoxifen citrate … …equivalent to tamoxifen....mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge film-coated dispersible tablets marked '20' on one side

Pharmacodynamics
Tamoxifen is the trans-isomer of a triphenylethylene derivative. It is a nonsteroidal antiestrogen which that competes with estrogen for estrogen receptor positive on breast cancer cells thereby preventing their growth. It displays a complex spectrum of oestrogen antagonist and oestrogen agonist-like pharmacological effects in different tissues. For example, tamoxifen acts as an estrogen receptor antagonist in the breast, but as an agonist in the uterus. Tamoxifen has been shown to up-regulate both estrogen and progesterone receptors in breast cancer.

Tamoxifen's estrogen-like influence on the skeletal and cardiovascular systems reduces postmenopausal bone loss and produces favorable cholesterol, lipid, and lipoprotein profiles.
Tamoxifen's anticancer activity was originally thought to be due solely to its ability to compete with estrogen for binding sites (estrogen receptors, ER) in target tissues such as the breast. However, other recognized actions include inhibition of protein kinase C and Ca(2+)-calmodulin-dependent cAMP phosphodiesterase, induction of cells surrounding the cancer cells to secrete the negative growth factor transforming growth factor-beta (TGF-beta), and suppression of insulin-like growth factor I (IGF-1), which is a potent mitogen for breast cancer cell in vitro .

Pharmacokinetics

Absorption
Tamoxifen is well absorbed from the gastrointestinal tract.
Peak plasma concentrations of tamoxifen occur 4 to 7 hours after an oral dose.

Distribution
It is extensively protein bound

Metabolism
It is extensively metabolised by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6. The major serum metabolite N-desmethyltamoxifen(active) which is formed mainly via CYP3A4; 4-Hydroxytamoxifen is a minor metabolite. N-Desmethyltamoxifen and 4-hydroxytamoxifen are further metabolised (via CYP2D6 and the CYP3A family, respectively) to 4-hydroxy-N-desmethyltamoxifen (endoxifen). Several of the metabolites are stated to have similar pharmacological activity to the parent compound, and endoxifen has been proposed as an alternative treatment to avoid differences in metabolism.

Elimination
Plasma clearance is reported to be biphasic and the terminal half-life may be up to 7 days. Tamoxifen is excreted slowly in the faeces, mainly as conjugates. Small amounts are excreted in urine. Tamoxifen appears to undergo enterohepatic circulation
N-desmethyltamoxifen has a half-life at steady state of about 14 days.

Indication

Tamoxifen is indicated for the treatment of breast cancer.

Recommended Dosage

Adults (including elderly): The dosage range is 20 to 40 mg daily, given either in divided doses twice daily or as a single dose once daily.

Use in children
The use of tamoxifen is not recommended in children, as safety and efficacy have not been established

Mode of Administration
Oral

Contraindications
Tamoxifen must not be given during pregnancy. Premenopausal patients must be carefully examined before treatment to exclude the possibility of pregnancy

Hypersensitivity to the product or any of its ingredients

When used for the reduction in breast cancer incidence in high risk women and women with Ductal Carcinoma in Situ with

- concomitant coumarin-type anticoagulant therapy
- history of deep vein thrombosis
- history of pulmonary embolus

Warnings and Precautions

- Menstruation is suppressed in a proportion of premenopausal women receiving tamoxifen for the treatment of breast cancer.
- Uterine malignancies; risk of potentially fatal uterine sarcoma and endometrial carcinoma; risk increases with long-term use
- Endometrial changes including hyperplasia and polyps; increased risk

*Any patient receiving or having previously received Tamoxifen, who report abnormal gynaecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

- fibroids, uterine, endometriosis; increased risk
- liver abnormalities; fatty liver, cholestasis, hepatitis, and hepatic necrosis, some fatal, have been reported
- liver enzyme levels; changes have been observed
- metastatic breast cancer; hypercalcemia has been reported in some patients with bone metastases
- ocular disturbances including cataracts (some requiring surgery), corneal changes, decrease in color vision perception, retinal vein thrombosis, and retinopathy; increased risk
- premenopausal patients with advanced breast cancer; increased risk of ovarian cysts

- Prescribers should obtain careful histories with respect to the patient's personal and family history of Venous thromboembolism. If suggestive of a prothrombotic risk, patients should be screened for thrombophilic factors. Patients who test positive should be counselled regarding their thrombotic risk. The decision to use tamoxifen in these patients should be based on the overall risk to the patient. In selected patients, the use of tamoxifen with prophylactic anticoagulation may be justified

- thromboembolic events, including stroke, deep vein thrombosis, and pulmonary embolism; increased risk
- Increased risk for Venous thromboembolism (VTE) has been demonstrated in healthy tamoxifen- treated women .The risk of VTE is further increased by severe obesity, increasing age and all other risk factors for VTE. The risks and benefits should be

carefully considered for *all* patients before treatment with tamoxifen. This risk is also increased by concomitant chemotherapy . Long-term anticoagulant prophylaxis may be justified for some patients who have multiple risk factors for VTE.

- Surgery and immobility: Tamoxifen treatment should only be stopped if the risk of tamoxifen-induced thrombosis clearly outweighs the risks associated with interrupting treatment. All patients should receive appropriate thrombosis prophylactic measures and should include graduated compression stockings for the period of hospitalisation, early ambulation, if possible, and anticoagulant treatment.

- If any patient presents with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. The decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients, the continued use of tamoxifen with prophylactic anticoagulation may be justified.

Effects on the ability to drive and use machines
There is no evidence that tamoxifen results in impairment of these activities

Interactions with Other Medicaments

- There is a risk of increased anticoagulant effect if tamoxifen is given with coumarin anticoagulants. Conversely, use with cytotoxic drugs may increase the risk of thromboembolic events; prophylactic anticoagulation should be considered. In order to avoid bleeding during a possible thrombocytopenic episode, platelet aggregation inhibitors should not be used with tamoxifen.
- Tamoxifen increases the dopaminergic effect of bromocriptine; bromocriptine increases serum concentrations of tamoxifen and its major metabolite N-desmethyltamoxifen. Use with inhibitors of cytochrome P450 isoenzyme CYP2D6 has been shown to reduce plasma concentrations of endoxifen, a tamoxifen metabolite; while the clinical relevance is unclear, a reduced effect of tamoxifen cannot be excluded, and use with potent CYP2D6 inhibitors should be avoided if possible.
- Tamoxifen is metabolised by CYP3A4 and care is required when it is used with CYP3A4 inducers (such as rifampicin), as tamoxifen concentrations may be reduced; plasma concentrations of tamoxifen may be increased by use with CYP3A4 inhibitors.
- Preparations of sex hormones, especially oestrogens, should not be used with tamoxifen as a mutual decrease in effect is possible. Medroxyprogesterone decreases concentrations of N-desmethyltamoxifen, but not of tamoxifen.

- Tamoxifen is metabolised by cytochrome P450 isoenzymes, including CYP2D6 , and drugs which inhibit CYP2D6 can reduce metabolism and potentially increase the risk of breast cancer recurrence.
- Potent inhibitors should be avoided; these include the SSRIs paroxetine, fluoxetine, bupropion, and duloxetine, and other drugs such as perphenazine, pimozide, thioridazine, quinidine, ticlopidine, terbinafine, and cinacalcet.
- Weak to moderate inhibitors should be used with caution, especially in patients considered to be CYP2D6 intermediate metabolisers. These include the SSRIs sertraline, citalopram, and fluvoxamine, the tricyclic antidepressants clomipramine, doxepin, desipramine, imipramine, amitriptyline, and nortriptyline, as well as other drugs such as chlorpromazine, fluphenazine, haloperidol, amiodarone, amlodipine, felodipine, nicardipine, nifedipine, verapamil, chloroquine, halofantrine, ritonavir, cimetidine, clemastine, diphenylpyraline, hydroxyzine, promethazine, tripelennamine, and celecoxib

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

Concurrent use of following drugs and tamoxifen may result in decreased plasma concentrations of the active metabolites of tamoxifen

- cimetidine
- quinidine
- diphenhydramine,
- mifepristone
- thioridazine

Concurrent use of St John's Wort and tamoxifen may result in reduced tamoxifen effectiveness.

Concurrent use of tamoxifen and mitomycin may result in increased risk of hemolytic uremic syndrome.

Concurrent use of letrozole and tamoxifen may result in reduced letrozole serum concentrations.

Concurrent use of clobazam and tamoxifen may result in increased tamoxifen plasma concentrations.

Concurrent use of anastrozole and tamoxifen may result in reduced anastrozole plasma levels.

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Concurrent use of clopidogrel and tamoxifen may result in an increased risk of tamoxifen toxicity (nausea, vomiting, dizziness, hyperreflexia, qt prolongation, increase in liver function tests).

Statement on Usage During Pregnancy and Lactation

Pregnancy

Although there are no adequate and well-controlled studies of tamoxifen use in pregnant women, there have been a few reports of spontaneous abortions, birth defects, fetal deaths, and vaginal bleeding associated with tamoxifen use during pregnancy. Therefore, if tamoxifen is administered during pregnancy or if the patient becomes pregnant while receiving tamoxifen or within 2 months after therapy discontinuation, the woman should be informed of the potential risks to the foetus . Women should be advised not to become pregnant whilst taking tamoxifen and should use barrier or other non-hormonal contraceptive methods if sexually active. For women who are sexually active and of childbearing potential initiate tamoxifen during menstruation. If menstruation is irregular, a negative pregnancy test (beta-hCG) immediately before starting tamoxifen treatment should be adequate.

Lactation

It is not known whether tamoxifen is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. Tamoxifen has been shown to significantly inhibit postpartum lactation. Because tamoxifen exposure has the potential to cause harm in a nursing infant, nursing mothers who are on tamoxifen therapy should not breastfeed. The decision either to discontinue nursing or discontinue tamoxifen should take into account the importance of the drug to the mother.

Adverse Effects / Undesirable Effects

When side effects are severe, it may be possible to control them by a simple reduction of dosage (to not less than 20 mg/day) without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop the treatment.

Dermatologic: Menopausal flushing, skin rashes (including rare reports of erythema multiforme, Stevens-Johnson syndrome, cutaneous vasculitis, and bullous pemphigoid) dry skin and alopecia,

Reproductive: Irregular periods, vaginal discharge vaginal bleeding pruritus vulvae, uterine cancer, uterine fibroids and endometrial changes including hyperplasia and polyps may occur, and an increased incidence of endometrial carcinoma, and rarely uterine sarcoma, has been reported. Suppression of menstruation may occur in premenopausal women and cystic ovarian swellings have occasionally occurred.

Endocrine metabolic: Breast cancer, contralateral

Hepatic: Tamoxifen has been associated with increased liver enzymes, and rarely with cholestasis and hepatitis.

Gastrointestinal: nausea, gastrointestinal intolerance

Neurologic: dizziness, headache, depression, confusion

Haematologic: Thromboembolic disorder/events; deep venous thrombosis. Transient thrombocytopenia and leucopenia have been reported
*When Tamoxifen is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

Ophthalmic: Cataract, visual disturbances (blurred vision and loss of visual acuity, corneal opacities, retinopathies, and cataracts have occurred rarely)

*Cases of optic neuropathy and optic neuritis have been reported in patients receiving tamoxifen and, in a small number of cases, blindness has occurred

Respiratory: Interstitial pneumonitis, pulmonary embolism

Other: Breast cancer; receptor-negative, uterine cancer, fatigue, hypertriglyceridaemia in some cases with pancreatitis, fluid retention, muscle cramps, hypersensitivity reactions, including angioedema.Tumour pain and flare may be a sign of response, but hypercalcaemia, sometimes severe, has developed in patients with bony metastases.

Overdose and Treatment
Symptoms

Overdoses are extremely rare; however, as they are widely used, adverse effects are common. There is very little information regarding overdose of these compounds in humans. At doses 6 times (400 mg/m(2) the recommended doses (20 to 40 mg daily), neurotoxicity (seizures, tremor, hyperreflexia, unsteady gait, and dizziness) and ECG changes (prolonged QT interval) were noted.

Treatment
There is no specific antidote to overdosage and treatment must be symptomatic.

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Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]

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