

Data Sheet

GENOX

10mg & 20mg tablets

Tamoxifen citrate

Presentation

Each GENOX 10 tablet contains 10mg of Tamoxifen citrate. GENOX 10 is presented as white, biconvex, tablets, marked "TN: 10" on one side and G on the reverse.

Each GENOX 20 tablet contains 20mg of Tamoxifen citrate. GENOX 20 is presented as white, biconvex tablets, marked "TN: breakline:20" on one side and G on the reverse.

Uses

Actions

GENOX (tamoxifen) is a non-steroidal, triphenylethylene-based medicine which displays a complex spectrum of oestrogen antagonist and oestrogen agonist-like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an anti-oestrogen, preventing oestrogen binding to the oestrogen receptor. In women with oestrogen receptor-positive/unknown breast tumours, adjuvant tamoxifen has been shown to significantly reduce recurrence of the disease and improve 10-year survival, achieving a significantly greater effect with five years treatment than with 1 or 2 years treatment. These benefits appear to be largely irrespective of age, menopausal status, tamoxifen dose and additional chemotherapy. However, clinical studies have also shown some benefit in oestrogen receptor negative tumours in patients both with early and advanced disease which may indicate other mechanisms of action. In the clinical situation, it is recognised that tamoxifen leads to reductions in levels of blood total cholesterol and low density lipoproteins in postmenopausal women of the order of 10 to 20%. Additionally, tamoxifen has been reported to lead to maintenance of bone mineral density in postmenopausal women.

Pharmacokinetics

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4 to 7 hours. Steady state concentrations (about 300 nanogram/mL) are achieved after four weeks treatment with 40mg daily. The medicine is highly protein bound to serum albumin (>99%). Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect. Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the medicine itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

Indications

GENOX is indicated for:

1. The treatment of breast cancer. The response is similar to that seen with either oestrogens or androgens but tamoxifen appears to produce less marked side effects and to be more acceptable to the patient.
 2. The treatment of endometrial cancer.
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Dosage and Administration

Adults (including Elderly):

Breast cancer:

The dosage range is 20 to 40mg daily given either in divided doses twice daily or as a single dose once daily. In early disease, it is currently recommended that treatment is given for not less than 5 years. The optimal duration of tamoxifen therapy remains to be determined.

Endometrial cancer:

The dosage range is 20 to 40mg daily given either in divided doses twice daily or as a single dose once daily.

Children

Tamoxifen is not indicated for use in children.

Contraindications

GENOX must not be administered during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal deaths after women have taken tamoxifen, although no causal relationship has been established (see Warnings and Precautions: Pregnancy).

Tamoxifen should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.

Warnings and Precautions

Menstruation is suppressed in a proportion of pre-menopausal women receiving tamoxifen for the treatment of breast cancer.

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the oestrogen-like effect of tamoxifen. Any patients receiving or having previously received tamoxifen, who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated. Any patients receiving or having previously received tamoxifen, should be asked to report promptly to their doctor the following signs and symptoms which may be suggestive of the presence of endometrial cancer:

1. Abnormal vaginal bleeding such as:

- Bleeding between periods
- Heavier than normal bleeding
- Bleeding after menopause.

2. Changes in vaginal discharge.

3. Lower abdominal pain or pressure.

These patients should be promptly investigated.

According to one study, women who have taken unopposed oestrogen therapy, who are obese, or who are continuing to take tamoxifen after therapy for ≥ 5 years may be at greater risk for endometrial cancer and consideration should be given to closer monitoring of these groups.

No mutagenic effects have been seen.

Tamoxifen was not mutagenic in a range of *in vitro* and *in vivo* mutagenicity tests. Tamoxifen was genotoxic in some *in vitro* tests and *in vivo* genotoxicity tests in rodents. Gonadal tumours in mice and liver tumours in rats receiving tamoxifen have been reported in long-term studies. The clinical significance of these findings has not been established.

Effects on reproductive functions are expected from the anti-oestrogenic properties of the medicine. In the rat, uterine pressure effects (deformation of rib cage and altered cranial ossification patterns) have been ascribed to inhibition of the action of oestrogens on the uterus, but these simple deformations disappear after birth. In pregnant marmosets dosed during organogenesis or in the last half of pregnancy, no deformations were seen.

A number of second primary tumours, 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.

Retinopathy and keratopathy may occur and patients should be asked to report the following symptoms of ocular damage without delay:

- Blurred vision lasting more than 2 weeks
- Change in colour vision.

Patients reporting these symptoms should be referred for ophthalmological examination. The ocular damage caused by tamoxifen is characterised by a reduction in visual acuity, bilateral macular oedema and yellow ringlike deposits in the paramacular and fovea areas. If tamoxifen is withdrawn promptly the vision usually returns to normal without permanent impairment.

Pregnancy:

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

In rodent models of foetal reproductive tract development, tamoxifen was associated with changes similar to those caused by oestradiol, ethinyloestradiol, 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 whilst taking GENOX and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal patients must be carefully examined before treatment to exclude pregnancy. Women should be informed of the potential risks to the foetus, should they become pregnant whilst taking GENOX or within two months of cessation of therapy.

Lactation:

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

Effect on ability to drive or operate machinery:

There is no evidence that tamoxifen results in impairment of these activities.

Adverse Effects

During long term treatment, side effects are not as numerous or as serious with tamoxifen as with the androgens and oestrogens which are also used to treat breast cancer. Those that have been reported can be classified as either due to the pharmacological action of the medicine, e.g. hot flushes, vaginal bleeding, vaginal discharge and pruritus vulvae and tumour flare or as more general side effects, e.g. gastrointestinal intolerance, headache, lightheadedness, and, occasionally, fluid retention and alopecia.

When such side effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dose range) without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop the treatment.

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

A small number of patients with bony metastases developed hypercalcaemia on initiation of therapy.

Falls in platelet count, usually only to 80,000-90,000/mm³, but occasionally lower, have been reported in patients taking tamoxifen for breast cancer.

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.

Cystic ovarian swellings have occasionally been observed in pre-menopausal women receiving tamoxifen.

An increase incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment.

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

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism during tamoxifen therapy. When tamoxifen is used in combination with cytotoxic agents, there is a further increase in the risk of thromboembolic events occurring.

Very rarely, cases of interstitial pneumonitis have been reported.

Tamoxifen has been associated with changes in liver enzyme levels and on rare occasions with a spectrum of more severe liver abnormalities, including fatty liver, cholestasis and hepatitis.

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

Interactions

When tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such co-administration is initiated, careful monitoring of the patient is recommended.

When tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see Adverse Effects).

The known principal pathway for tamoxifen metabolism in humans is demethylation, catalysed by CYP3A4 enzymes. Pharmacokinetic interactions with the CYP3A4 inducing agent rifampicin, showing a reduction in tamoxifen plasma levels have been reported in the literature. The relevance of this to clinical practice is not known.

Overdosage

On theoretical grounds an overdosage would be expected to cause an enhancement of the pharmacological side effects. Animal studies have shown that extreme overdosage (100 to 200 times the recommended daily dose) may produce oestrogenic effects. There is no specific antidote and treatment must be symptomatic.

Pharmaceutical Precautions

GENOX tablets should be protected from light. Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Blister packs of GENOX 10 contain 30 x 10mg tablets
Blister packs of GENOX 10 contain 60 x 10mg tablets
Blister packs of GENOX 10 contain 100 x 10mg tablets

Blister packs of GENOX 20 contain 30 x 20mg tablets Blister packs of GENOX 20 contain 60 x 20mg tablets

Blister packs of GENOX 20 contain 100 x 20mg tablets

Not all pack sizes may be marketed

Further Information

Excipients present in the tablets are mannitol, maize starch, croscarmellose sodium and magnesium stearate.

Name and Address

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Date of Preparation

2 December 2009