

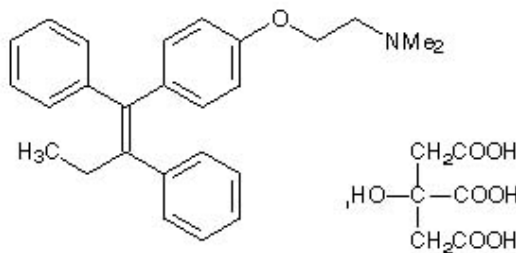
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Tamoxifen (as citrate)

Chemical name: *trans*-1-[4-(2-dimethylaminoethoxy)phenyl]1,2-diphenyl-1-butene

Structural formula:



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

Molecular weight: 563.6

CAS Registry No.: 54965-24-1

DESCRIPTION

Tamoxifen citrate is a white or almost white, crystalline powder, slightly soluble in water, soluble in methanol, slightly soluble in acetone.

Each Genox tablet contains the active ingredient tamoxifen citrate equivalent to 10 mg or 20 mg of tamoxifen. The tablets also contain the following inactive ingredients: mannitol, starch – maize, croscarmellose sodium and magnesium stearate. *The tablets are gluten free.*

PHARMACOLOGY

Tamoxifen is a non-steroidal triphenylethylene based drug 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. However, clinical studies have shown some benefit in oestrogen receptor negative tumours in patients older than 50 years which may indicate other mechanisms of action.

Pharmacokinetics

Absorption. Tamoxifen is absorbed from the gastrointestinal tract, however the site and extent of absorption is not known. Peak serum levels of 15 to 25 nanogram/mL were observed three to six hours after administration of a single oral dose of 10 mg tamoxifen. Steady state serum levels are achieved after

approximately 4 weeks therapy. Mean steady state values after dosing at 20 mg twice daily were 285 ± 19 nanogram/mL and 477 ± 35 nanogram/mL for tamoxifen and N-desmethyltamoxifen respectively. There is no information available on the bioavailability of tamoxifen.

Distribution. Little information is available in humans. It has been found in the uterus and ovary, particularly in the endometrium and corpus luteum. Radioactivity studies in animals show high levels in the liver, lung, ovary and spleen. Low levels have been found in the pituitary, eyes and brain.

Tamoxifen appears to be bound to an unknown degree to cytoplasmic protein receptors in all oestrogen target tissues, and is highly protein bound to serum albumin (>99%).

Metabolism. Tamoxifen undergoes extensive metabolism in the liver by hydroxylation, demethylation, and conjugation, giving rise to several metabolites. The major circulating metabolite of tamoxifen in serum is N-desmethyltamoxifen, which has a pharmacological profile very similar to that of tamoxifen and thus contributes to the therapeutic effect. Other minor metabolites are formed, some of which also have anti-oestrogenic activity.

Excretion. The elimination of tamoxifen and its major metabolite N-desmethyltamoxifen is slow. This leads to extensive accumulation of both compounds in serum during chronic administration. Tamoxifen is mainly excreted via the faeces, with only small amounts appearing in the urine. The drug is excreted mainly as its conjugates. In one patient studied for 13 days after dosing, approximately 50% of the dose had been excreted in the faeces, and 13% in the urine. In animals, tamoxifen undergoes enterohepatic circulation, and is thought to do so in humans.

The elimination half-life of tamoxifen is estimated to be 5 to 7 days and 10 to 14 days for N-desmethyltamoxifen.

Clinical Implications of Pharmacokinetic Data

As the main site of metabolism is the liver and accumulation of the drug and its active metabolites is possible with prolonged treatment, dose and dosing intervals may need adjustment in patients with liver disease.

INDICATIONS

Treatment of breast cancer.

CONTRAINDICATIONS

Tamoxifen must not be given during pregnancy.

Pre-menopausal patients must be carefully examined before treatment for breast cancer to exclude the possibility of pregnancy.

Genox should not be given to patients who have experienced hypersensitivity to tamoxifen or any of its ingredients.

PRECAUTIONS

Endometrial Changes. An increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) have been reported in association with tamoxifen treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the oestrogenic properties of tamoxifen. Any patients receiving, or having previously received Genox who report abnormal gynaecological symptoms, especially vaginal bleeding should be promptly investigated.

Uterine Cancer. In a large randomised trial in Sweden of adjuvant tamoxifen 40 mg/day for 2 to 5 years, an increased incidence of uterine cancer was noted. Twenty-three of 1,372 patients randomised to receive tamoxifen versus 4 of 1,357 patients randomised to the observation group developed cancer of the uterus [RR=5.6; (1.9-16.2), p<0.001].

One of the patients with cancer of the uterus who was randomised to receive tamoxifen never took the drug. After approximately 6.8 years of follow-up in the ongoing NSABP B-14¹ trial, 15 of 1,419 women randomised to receive tamoxifen 20 mg/day for 5 years developed uterine cancer and 2 of the 1,424 women randomised to receive placebo, who subsequently had recurrent breast cancer and were treated with tamoxifen, also developed uterine cancer. Most of the uterine cancers were diagnosed at an early stage, but deaths from uterine cancer have been reported. Patients receiving Genox should have routine gynaecological care and report any abnormal vaginal bleeding to their physician.

Ocular Changes. Cases of visual disturbances, including infrequent reports of corneal changes, and common reports of retinopathy have been described in patients receiving tamoxifen therapy. Cataracts have commonly been reported in association with the administration of tamoxifen.

Haematological Effects. Tamoxifen should be used cautiously in patients with existing leucopenia or thrombocytopenia. 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 and very rarely cases of agranulocytosis have been reported. Decreases in platelet counts, usually 50,000 to 100,000/mm³, infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. Periodic complete blood counts, including platelet counts, may be appropriate.

Second Primary Tumours. 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.

Use in Premenopausal Women. It should be noted that only a small number of premenopausal women have

¹ The NSABP (National Surgical Adjuvant Breast and Bowel Project B-14 trial is undergoing reaudit and information from this study may be subject to change.

been treated, since candidates for therapy are usually postmenopausal, either reaching a natural menopause, or having menopause induced by surgery or radiotherapy. Menstruation is suppressed in a proportion of premenopausal women receiving tamoxifen for the treatment of breast tumours.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 relevance of these findings has not been established.

Use in Pregnancy (Category B3)

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.

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. Although the clinical relevance of these changes is unknown, some of them, and especially vaginal adenosis, are similar to those seen in young women who were exposed to diethylstilboestrol *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 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.

Australian categorisation definition of Category B3. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

It is not known if tamoxifen is excreted in human milk. The drug is therefore not recommended during lactation.

Paediatric Use

Genox is not indicated for use in children.

Interactions with Other Medicines

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

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

The known principal pathway for tamoxifen metabolism in humans is demethylation, catalysed by CYP3A4 enzymes. Pharmacokinetic interaction with the CYP3A4 inducing agent rifampicin, showing a reduction in tamoxifen plasma levels has been reported in the literature.

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen has been reported in the literature. This showed a reduction in plasma level of active tamoxifen metabolite, 4-hydroxy-N-desmethyltamoxifen. Reduced efficacy on tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine).

ADVERSE EFFECTS

The adverse reactions which have been reported are of two types:

- those associated specifically with the pharmacological action of the drug, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae; tumour pain and tumour flare
- those of a more general nature, e.g. gastrointestinal intolerance, headache, lightheadedness, and occasionally, fluid retention and alopecia.

In patients treated with tamoxifen for metastatic breast cancer, the most frequent adverse reactions are hot flushes, nausea and vomiting. These may occur in up to 25% of patients. Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, alopecia and increased bone and tumour pain. Other adverse reactions which are seen infrequently are hypercalcaemia, peripheral oedema, pruritus vulvae, dizziness and lightheadedness. Infrequent cases of endometrial, ocular and haematological adverse effects have been reported (see **PRECAUTIONS**).

When adverse reactions 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 adverse reactions 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 commonly hypersensitivity reactions, including angioedema, have been reported.

There is evidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis and pulmonary embolism, occurring commonly during tamoxifen therapy. When Genox is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

Uncommonly, cases of interstitial pneumonitis have been reported.

Leg cramps have been reported commonly in patients receiving tamoxifen.

Although hypercalcaemia may occur in patients with advanced breast cancer, uncommonly patients with bony metastases have developed hypercalcaemia on initiation of therapy with tamoxifen.

Tamoxifen has been associated with changes in liver enzyme levels and with a spectrum of more severe liver abnormalities which in some cases were fatal, including fatty liver, cholestasis and hepatitis, liver failure, cirrhosis and hepatocellular injury (including hepatic necrosis).

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

Uterine fibroids and endometrial changes including hyperplasia and polyps have been reported. Cystic ovarian swelling has occasionally been observed in premenopausal women receiving tamoxifen.

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

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

DOSAGE AND ADMINISTRATION

Adults. The initial dose is 20 mg (two Genox 10 tablets or one Genox 20 tablet) once daily. In advanced breast cancer, if no response is seen, dosage should be increased to 40 mg (four Genox 10 tablets or two Genox 20 tablets) once daily.

Children. Genox is not indicated for use in children.

Hepatic Insufficiency. (see **PHARMACOLOGY - Pharmacokinetics; Clinical Implications of Pharmacokinetic Data**).

OVERDOSAGE

On theoretical grounds an overdosage would be expected to cause enhancement of the pharmacological side effects mentioned above. Observations in animals show that extreme overdosage (100 to 200 times the equivalent of the recommended daily human dose) may produce oestrogenic effects.

There have been reports in the literature that tamoxifen given at several times the standard dose may be

associated with prolongation of the QT interval of the ECG.

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

Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Genox 10 10 mg tablet: white, convex, marked TN on one side, G on reverse; blister pack 60s.

10

Genox 20 20 mg tablet: white, scored, convex, marked TN on one side, G on reverse; blister pack 60s.

20

Store below 25°C. Protect from heat and light.

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

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Glebe NSW 2037

(ABN 93 002 359 739)

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DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 16 July 2007.

Date of most recent amendment: 1 September 2010.