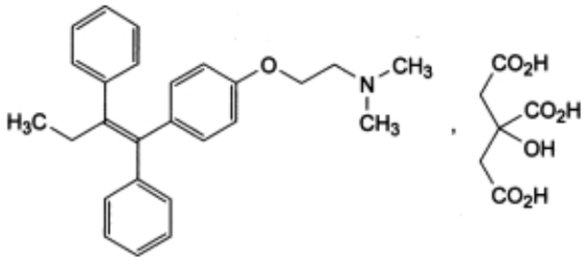
NOLVADEX®

tamoxifen

PRODUCT INFORMATION

NAME OF THE MEDICINE

Tamoxifen citrate.



$C_{26}H_{29}NO,C_6H_8O_7$ MW: 563.6

CAS No: *54965-24-1*

DESCRIPTION

NOLVADEX (tamoxifen) is the trans-isomer of 1-[4-(2-dimethylaminoethoxy) phenyl]-1,2-diphenyl-1-butene.

NOLVADEX (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 antioestrogen, preventing oestrogen binding to the oestrogen receptor.

PHARMACOLOGY

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.

Bioavailability

No information available.

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.

Protein Binding

The drug 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 humans 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 antioestrogenic 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.

In a clinical study where girls between 2 and 10 years with McCune Albright Syndrome (MAS) received 20 mg tamoxifen once a day for up to 12 months duration, there was an age-dependent decrease in clearance and an increase in exposure (AUC), (with values up to 50% higher in the youngest patients) compared with adults.

Half-Life

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 interval may need adjustment in patients with liver disease.

INDICATIONS

NOLVADEX is indicated for the treatment of breast cancer.

CONTRAINDICATIONS

NOLVADEX must not be given during pregnancy. Premenopausal patients must be carefully examined before treatment for breast cancer to exclude the possibility of pregnancy.

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

PRECAUTIONS

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

In a large randomized trial in Sweden of adjuvant NOLVADEX 40 mg/day for 2-5 years, an increased incidence of uterine cancer was noted. Twenty three of 1,372 patients randomized to receive NOLVADEX versus 4 of 1,357 patients randomized 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 randomized to receive NOLVADEX never took the drug. After approximately 6.8 years of follow-up in the ongoing NSABP B-14[1] trial, 15 of 1,419 women randomized to receive NOLVADEX 20 mg/day for 5 years developed uterine cancer and 2 of the 1,424 women randomized to receive placebo, who subsequently had recurrent breast cancer and were treated with NOLVADEX, 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 NOLVADEX should have routine gynaecological care and report any abnormal vaginal bleeding to their physician.

In an uncontrolled trial in 28 girls aged 2-10 with McCune Albright Syndrome (MAS), who received 20mg once a day for up to 12 months duration, mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established. Tamoxifen is not approved for treatment of McCune Albright Syndrome.

In delayed microsurgical breast reconstruction NOLVADEX may increase the risk of microvascular flap complications.

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

[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.

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.

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.

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

NOLVADEX should be used cautiously in patients with existing leucopenia or thrombocytopenia. Leucopenia has been observed following the administration of NOLVADEX sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe and rarely cases of agranulocytosis have been reported. Decreases in platelet counts, usually to 50,000 to 100,000/mm^3, infrequently lower, have been occasionally reported in patients taking NOLVADEX for breast cancer. Periodic complete blood counts, including platelet counts, may be appropriate.

Use in Premenopausal Women

It should be noted that only a small number of premenopausal women have 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 NOLVADEX for the treatment of breast tumours. Cystic ovarian swellings have occasionally been observed in women receiving NOLVADEX.

Use in Pregnancy (Category B3)

NOLVADEX 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 NOLVADEX, 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, ethynyloestradiol, 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 NOLVADEX 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 NOLVADEX or within two months of cessation of therapy.

Use in Lactation

It is not known if NOLVADEX is excreted in human milk and therefore the drug is not recommended during lactation.

Interactions with other medicines

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

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

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 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 and those of a more general nature, e.g. gastrointestinal intolerance, headache, light-headedness and, occasionally, fluid retention and alopecia. In patients treated with NOLVADEX for metastatic breast cancer, the most frequent adverse reactions are hot flushes, nausea and vomiting. These may occur in up to one-fourth 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, pruritis vulvae, dizziness and light-

headedness. Infrequent cases of endometrial, ocular and haematological adverse effects have been reported (see PRECAUTIONS). When such 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, cutaneous vasculitis, and bullous pemphigoid) and commonly hypersensitivity reactions, including angioedema have been reported.

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

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.

Cystic ovarian swellings have occasionally been observed in premenopausal women receiving NOLVADEX. Vaginal polyps have rarely been observed in women receiving NOLVADEX

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

Uncommonly, cases of interstitial pneumonitis have been reported.

Leg cramps and myalgia have been reported commonly in patients receiving NOLVADEX.

NOLVADEX has been associated with changes in liver enzyme levels andwith 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 NOLVADEX.

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

Cutaneous lupus erythematosus has been observed very-rarely in patients receiving NOLVADEX.

Porphyria cutanea tarda has been observed very-rarely in patients receiving NOLVADEX.

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

Sensory disturbances (including paraesthesia and dysgeusia) have been reported commonly in patients receiving NOLVADEX.

DOSAGE AND ADMINISTRATION

Adults

The initial dose is 20 mg (two NOLVADEX tablets, or one NOLVADEX-D tablet) once daily. In advanced breast cancer, if no response is seen, dosage may be increased to 40 mg (four NOLVADEX tablets, or two NOLVADEX-D tablets) once daily.

Children

NOLVADEX is not indicated for use in children.

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 NOLVADEX 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 symptomatic.

PRESENTATION AND STORAGE CONDITIONS

NOLVADEX is presented as white to off-white, round, biconvex film coated tablets, impressed with "NOLVADEX 10" on one face, and plain on the reverse face. NOLVADEX tablets each contain tamoxifen citrate (15.2 mg) equivalent to 10 mg of tamoxifen.

NOLVADEX-D is presented as white to off-white, octagonal shaped, biconvex film coated tablets, impressed with "NOLVADEX-D" on one face, and plain on the reverse face. NOLVADEX-D tablets each contain tamoxifen citrate (30.4 mg) equivalent to 20 mg of tamoxifen.

Both NOLVADEX and NOLVADEX-D also include the following excipients: starch - maize, lactose, croscarmellose sodium, gelatin, magnesium stearate, hypromellose, macrogol 300, titanium dioxide.

NOLVADEX and NOLVADEX-D tablets should be protected from light. .

NOLVADEX (10 mg): blister-packed in strips of 10, in containers of 30.*

NOLVADEX-D (20 mg): blister-packed in strips of 10, in containers of 30.

NOLVADEX and NOLVADEX-D tablets should be protected from light. Store below 30°C.

NAME AND ADDRESS OF SPONSOR

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NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of TGA Approval - 22 May 2007

Date of most recent amendment – 27 August 2012

NOLVADEX and NOLVADEX-D is a trademark of the AstraZeneca group of companies

* Not marketed