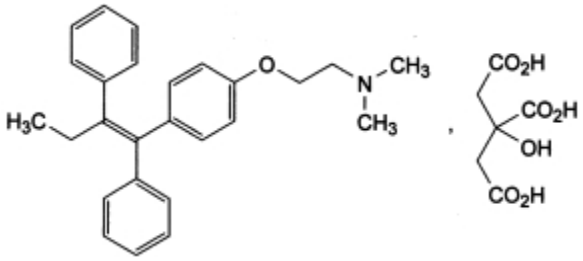
NOLVADEX®

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.

CLINICAL TRIALS

Primary reduction of breast cancer risk

The breast cancer primary risk reduction trials include the International Breast Cancer Intervention Study (IBIS-1), the National Surgical Adjuvant Breast and Bowel Project P1 study (NSABP P1), and the Royal Marsden Hospital chemoprevention trial (Royal Marsden). All trials were double-blind placebo-controlled randomised trials of oral tamoxifen (20 mg per day) for the primary reduction of breast cancer risk in women at increased risk of breast cancer. Women were treated for 5 years (IBIS-1 and NSABP P1) or 8 years (Royal Marsden) and followed for up to 20 years.

The IBIS-1, NSABP P1, and Royal Marsden trials all defined breast cancer risk differently, and recruited women with both moderate or high lifetime risk: IBIS-I included women with a two-fold relative risk if they were aged 45 to 70 years, a four-fold relative risk if they were aged 40 to 44 years, or a ten-fold relative risk if they were aged 35 to 39 years; NSABP P1 included women aged ≥60 years or aged 35 to 59 years with a 5-year predicted risk for breast cancer of at least 1.66% as determined using a modified Gail's model or a history of lobular carcinoma in situ (LCIS) or atypical hyperplasia; and Royal Marsden included healthy women aged 30 to 70 years old with an increased risk of developing breast cancer based on family history.

All trials excluded women with breast cancer (apart from Lobular Carcinoma In Situ - LCIS), a history of invasive cancer, pregnancy, and current or past deep vein thrombosis or pulmonary embolism. Other relevant exclusion criteria included the current use of oral contraceptives (NSABP P1, Royal Marsden), recent or current hormone replacement therapy (NSABP P1), and current anticoagulant use (IBIS-I).

The majority of women in all trials were aged 59 years or below. NSABP P1 included the largest proportion of women aged 60 years or over (30%). In NSABP P1, the majority of women were white (96%); race was not reported in the other trials. A substantial proportion of women in all trials were premenopausal (46% in IBIS-I and 65% in Royal Marsden) or younger than 50 years old (37% NSABP P1).

Efficacy results from the trials are shown in tables 1 and 2. Table 1 includes results of a meta-analysis of individual participant data from over 28,000 women who were treated with tamoxifen or placebo for the primary reduction of breast cancer risk. The results of the individual trials were generally consistent with the findings in the meta-analysis and the risk reduction effects of tamoxifen lasted for more than 10 years after treatment ended. Table 2 shows the number needed to treat (NNT) to prevent a diagnosis of breast cancer based on the same data.

Table 1 Summary of Efficacy Results from the Primary Risk Reduction Trials

	Cuzick meta-analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
	Tamox n=14,192 Events	Placebo n=14,214 Events	Tamox n=3579 Events	Placebo n=3575 Events	Tamox n=6597 Events	Placebo n=6610 Events	Tamox n=1238 Events	Placebo n=1233 Events
	HR (95% CI)		HR (95% CI)		RR (95% CI)		HR (95% CI)	
All breast cancer	431	634	251	350	205	343	96	113
	0.67 (0.59-0.76)		0.71 (0.60-0.83)		NR		NS	
Invasive breast cancer	NR		214	289	145	250	38[e]	56[e]
			0.73 (0.61-0.87)		0.57 (0.46-0.70)		0.67 (0.44-1.01)[e]	
Non-invasive cancers	77	112	35	53	60	93	NR	
	0.72 (0.57-0.92)		0.65 (0.43-1.00)		0.63 (0.45-0.89)			
Oestrogen receptor-positive cancers	219	396	160	238	70	182	53	86
	0.56 (0.47-0.67)		0.66 (0.54-0.81)		0.38 (0.28-0.50)		0.61 (0.43-0.86)	
Oestrogen receptor-negative cancers	116	103	50	47	56	42	24	17
	NS		NS		NS		NS	

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = not significant, NR = not reported, placeb = placebo, RR = risk ratio, tamox = tamoxifen.

[a] Cuzick 2013 was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Royal Marsden primary risk reduction trials in women at increased risk of breast cancer, and the Italian trial in women at normal risk of breast cancer. The median follow up was 65 months.

[b] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 16 years.

[c] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 6 years

[d] Participants were treated with 20 mg tamoxifen for 8 years; the median follow up was 13 years

[e] Results shown for posttreatment period only. During treatment, invasive breast cancer incidence was not significantly different between the tamoxifen and placebo groups.

Table 2 Summary of Efficacy Results from the Primary Risk Reduction Trials - Numbers Needed to Treat (NNT)

	Cuzick meta-analysis		IBIS-I		NSABP P1		Royal Marsden	
	Tamox n=14,192	Placeb n=14,214	Tamox n=3579	Placeb n=3575	Tamox n=6597	Placeb n=6610	Tamox n=1238	Placeb n=1233
	NNT		NNT		NNT		NNT	
All breast cancer	71		37		NR		NS	
Invasive breast cancer	NR		48		64		NS	
Non-invasive cancers	408		199		202		NR	
Oestrogen receptor-positive	81		46		60		38	

Abbreviations: placeb = placebo, NNT = number needed to treat, NR = number of events or statistical analyses not reported, NS = not significant, tamox = tamoxifen.

In the health-related quality of life component of the NSABP-1 trial, which included 11,064 of the 13,388 women enrolled in the trial, vasomotor and gynaecological symptoms were reported more frequently in the tamoxifen group, consistent with the known safety profile of tamoxifen. Some sexual functioning symptoms were reported significantly more frequently in the tamoxifen group, but the differences were very small (mean differences between the treatment groups ranged from 0.54% to 1.24%).Tamoxifen did not increase the rate of depression or mental health problems in general, nor significantly increase the frequency of reported changes in body weight.

Mortality was a secondary outcome measure for the IBIS-1, NSABP P1 and Royal Marsden trials. In comparing the tamoxifen and placebo arms, no significant difference was found for mortality in each trial. This outcome may be due to confounding factors in these trials such as low event rates, underpowering, close screening leading to early detection of events and subsequent breast cancer treatments.

Concomitant use of Hormone Replacement Therapy

The IBIS-I trial found that tamoxifen was effective in reducing the risk of breast cancer in women who were not taking hormone replacement therapy. For women who did use hormone replacement therapy, there was no significant reduction in the risk of developing invasive breast cancers: 110 vs 124 (HR 0.88, 95% CI 0.68-1.13, p=0.31). These findings were consistent over the 20-year study period. In the NSABP P1 trial, women who were taking hormone replacement therapy were excluded from the trial. The Royal Marsden trial was not powered to demonstrate an effect.

Effects of age and menopausal status

No age-related effects of tamoxifen on breast cancer incidence were reported in the primary risk reduction trials. Analyses according to age were performed in the

final analyses of the IBIS-1 and the NSABP P1 trials. In the IBIS-I trial, breast cancer incidence was significantly decreased in the tamoxifen vs the placebo group in women aged ≤50 years and >50 years. In the NSABP P1 trial, invasive breast cancer incidence was significantly decreased in the tamoxifen vs the placebo group in women aged ≤49 years, 50 to 59 years, and ≥60 years. Thus, no age-related effects of tamoxifen on breast cancer incidence were reported in the trials.

Analyses according to menopausal status were performed in the 96-month analysis of the IBIS-1 trial. In the IBIS-I trial, tamoxifen significantly reduced the risk of breast cancer in premenopausal women compared with placebo. It should be noted that the IBIS-1 trial was not sufficiently powered to detect a difference specifically in postmenopausal women. In the NSABP P1 trial, the incidence of invasive breast cancer was significantly lower in the tamoxifen vs placebo group in women aged ≥60 years, who would have been postmenopausal (40 vs 80, RR 0.49, 95% CI 0.33-0.73).

Lobular carcinoma in situ and atypical hyperplasia

In NSABP P1, there was a 75% breast cancer risk reduction in women with a history of atypical hyperplasia compared with a 37% risk reduction in women with no history of atypical hyperplasia (RR 0.63, 95% CI 0.50-0.78). The risk reductions for women with and without lobular carcinoma in situ were similar.

INDICATIONS

Treatment of breast cancer

NOLVADEX is indicated for the treatment of breast cancer.

Primary reduction of breast cancer risk

NOLVADEX is indicated for the primary reduction of breast cancer risk in women either at moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average).

CONTRAINDICATIONS

NOLVADEX must not be given during pregnancy. In premenopausal women, the possibility of pregnancy must be excluded before starting tamoxifen.

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

When considered for primary reduction of breast cancer risk, NOLVADEX is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus.

PRECAUTIONS

General 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 non-menstrual 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.

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during NOLVADEX therapy. When NOLVADEX is coadministered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of NOLVADEX should be carefully considered in women with a history of thromboembolic events.

[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.

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 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 with caution 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.

Additional precautions relating to primary reduction of breast cancer risk

NOLVADEX therapy for this indication has uncommonly been associated with serious side effects such as pulmonary embolus and uterine cancer (both endometrial adenocarcinoma and uterine sarcoma). In trials comparing tamoxifen to placebo for reduction of the incidence of breast cancer in women at increased risk of breast cancer, the use of tamoxifen was associated with an increased risk of serious and sometimes fatal adverse events including endometrial cancer (approximately 4 cases per 1000 women over 5 years of use) and thromboembolic events (including deep vein thrombosis and pulmonary embolism). Less serious side effects such as hot flushes, vaginal discharge, menstrual irregularities and gynaecological conditions may also occur. Whether the benefits of treatment are considered to outweigh the risks depends on the woman's age, health history, and level of breast cancer risk (see CLINICAL TRIALS, PRECAUTIONS and ADVERSE EFFECTS).

Benign gynaecological conditions (including endometrial polyps, endometriosis, and ovarian cysts) and gynaecological procedures (including hysteroscopy, dilation and curettage, and hysterectomy) were also found to occur more frequently with tamoxifen use. Non-gynaecological conditions such as cataracts were also increased (see ADVERSE EFFECTS).

Any women receiving or having previously received NOLVADEX for risk reduction should be promptly investigated if any abnormal gynaecological symptoms develop, especially non-menstrual vaginal bleeding.

The risks of tamoxifen therapy are generally lower in younger women than in older women. In the primary risk reduction trials, women younger than 50 years did not have an increased risk of endometrial cancer or pulmonary embolism and the increased risk of deep vein thrombosis was small and restricted to the treatment period (see ADVERSE EFFECTS – Women under 50 years old). Women aged less than 30 years old were excluded from primary risk reduction trials so the efficacy and safety of tamoxifen treatment in these younger women is unknown.

When considered for primary reduction of breast cancer risk, NOLVADEX is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus (see CONTRAINDICATIONS). In women who do not have a history of thromboembolic events, but who are at increased risk of thromboembolic events, the benefits and risks of tamoxifen for the primary reduction of breast cancer risk should be carefully considered. Risk factors for thromboembolic events include smoking, immobility and a family history of venous thrombosis; an additional risk factor, is concomitant oral contraceptive or hormone replacement therapy, which is not recommended in women taking tamoxifen. In women receiving tamoxifen for primary reduction of breast cancer risk, tamoxifen should be stopped approximately 3 weeks before undergoing elective surgery to reduce the risk of thromboembolic events. Consideration should also be given to discontinuing tamoxifen during periods of immobility.

The use of tamoxifen for reduction of breast cancer risk has been associated with reduced bone density in premenopausal women. Whether this may result in an increased risk of fracture is not known. Pre-menopausal women taking tamoxifen for this reason should be advised regarding measures to maintain bone health.

Use in Premenopausal Women

Menstruation is suppressed in a proportion of premenopausal women receiving NOLVADEX. Ovarian cysts 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 (see CONTRAINDICATIONS).

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 for the treatment of breast cancer, careful monitoring of the patient is recommended. In women receiving tamoxifen for the primary reduction of breast cancer risk, the use of coumarin type anticoagulants is contraindicated (see CONTRAINDICATIONS).

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).

For the primary reduction of breast cancer risk, there is some evidence that hormone replacement therapy may reduce the effectiveness of tamoxifen, and the safety of concomitant use of tamoxifen and hormone replacement therapy or oral contraceptives is unknown. In women with breast cancer, the use of hormone replacement therapy or oral contraceptives to manage tamoxifen side effects is a relative contraindication.

Effects on ability to drive and operate machinery

Fatigue has been reported with the use of NOLVADEX. Therefore, caution should be observed when driving or operating machinery while such symptoms persist.

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 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 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.

Fatigue has been reported very commonly in patients taking NOLVADEX.

Radiation recall has been observed very rarely in patients receiving NOLVADEX.

Primary reduction of breast cancer risk

The most common adverse events reported from studies in women at increased risk of breast cancer, and occurring more frequently during treatment with tamoxifen than with placebo, were those associated specifically with the pharmacological action of tamoxifen such as vasomotor symptoms (hot flushes, night sweats), menstrual abnormalities\irregularities, vaginal discharge, and vaginal dryness.

A summary of the more serious adverse events reported during the primary risk reduction trials is shown in Table 3. Tamoxifen significantly increased the incidence of endometrial cancer, deep vein thrombosis, and pulmonary embolism compared with placebo, but the absolute increase in risk was small. The risk of developing cataracts was also significantly increased with tamoxifen.

Table 3 Summary of Adverse Events from the Primary Risk Reduction Trials

	Cuzick meta-analysis[a]		IBIS-I[b]		NSABP P1[c]		Royal Marsden[d]	
Risk factor	**Tamox n=14,192**	**Placeb n=14,214**	**Tamox n=3579**	**Placeb n=3575**	**Tamox n=6597**	**Placeb n=6610**	**Tamox n=1238**	**Placeb n=1233**
All-cause mortality	214 (1.5%)	218 (1.5%)	182 (5.1%)	166 (4.6%)	126 (1.9%)	114 (1.7%)	54 (4.4%)	54 (4.4%)
Endometrial cancer	67 (0.6%)	31 (0.3%)	29 (0.81%)	20 (0.56%)	53 (0.8%)	17 (0.3%)	13 (1.1%)	5 (0.41%)
Other cancers	372 (2.6%)	367 (2.6%)	351 (9.8%)	315 (8.8%)	178 (2.7%)	155 (2.3%)	64 (5.2%)	70 (5.7%)
Deep vein thrombosis	131 (1.0%)	82 (0.6%)	50 (1.4%)	29 (0.81%)	49 (0.74%)	34 (0.51)	13 (1.1%)	9 (0.73%)
Pulmonary embolism			30 (0.84%)	22 (0.62%)	28 (0.42%)	13 (0.20%)		
Stroke	NR	NR	30 (0.84%)	28 (0.78%)	71 (1.1%)	50 (0.76%)	10 (0.81%)	16 (1.3%)
Transient ischaemic attack	NR	NR	NR	NR	31 (0.47%)	34 (0.51%)	NR	NR
Ischaemic heart disease/ cardiovascular events	144 (1.1%)	130 (1.0%)	141 (3.9%)	153 (4.3%)	113 (1.7%)	109 (1.6%)	21 (1.7%)	26 (2.1%)
Myocardial infarction	NR	NR	13 (0.36%)	17 (0.48%)	43 (0.65%)	44 (0.67%)	NR	NR
Cataracts	654 (6.4%)	583 (5.7%)	67 (1.9%)[e]	54 (1.5%)[e]	574 (9.4%)[f]	507 (8.3%)[f]	12 (0.97)	3 (0.24%)
Fractures	731 (7.2%)	791 (7.8%)	240 (6.7%)[e]	235 (6.6%)[e]	80 (1.2%)	116 (1.8%)	28 (2.3%)	33 (2.7%)

Abbreviations: NR = not reported, placeb = placebo, tamox = tamoxifen.

[a] Cuzick 2013 was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Marsden primary risk reduction trials in women at increased risk of breast cancer, and the Italian trial in women at normal risk of breast cancer. The median follow up was 65 months.

[b] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 16 years.

[c] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was 6 years

[d] Participants were treated with 20 mg tamoxifen for 8 years; the median follow up was 13 years

[e] Results from earlier analysis; median follow up was 8 years

[f] Results from earlier analysis; n=6101 tamoxifen and 6131 placebo; the median follow up was 4 years.

Women under 50 years old

A meta-analysis of risk reduction trials stratified by age (Iqbal 2012) showed that while women over 50 years old at randomisation had a significantly increased risk of endometrial cancer compared with placebo (RR 3.32, 95% CI 1.95-5.67; p<0.0001), women aged under 50 years did not (RR 1.19, 95% CI 0.53-2.65; p=0.6). Similarly, women under 50 did not have a significantly increased risk of

pulmonary embolism compared with placebo (RR 1.16, 95% CI 0.55-2.43; p=0.60) and their risk of deep vein thrombosis was only significantly increased during the active treatment phase (RR 2.30, 95% CI 1.23-4.31; p=0.009) but not after treatment had ended.

Gynaecological conditions and procedures

In placebo controlled trials of the use of tamoxifen for the primary reduction of breast cancer risk, benign gynaecological conditions and procedures were more commonly reported with tamoxifen. The IBIS-1 trial found that in 3573 women taking tamoxifen compared to 3566 women on placebo, the following gynaecological conditions and procedures were more common in women taking tamoxifen: abnormal bleeding (842 v 678, p<0.0001); endometrial polyps (130 v 65, p<0.0001); ovarian cysts (101 v 42, p<0.0001); hysteroscopy (228 v 138, p<0.0001); pelvic ultrasound (209 v 132, p<0.0001); dilation and curettage (178 v 94, p<0.0001); hysterectomy (154 v 104, p=0.002) and oophorectomy (103 v 67, p=0.006).

DOSAGE AND ADMINISTRATION

Adults

Treatment of breast cancer

The initial dose is 20 mg once daily. In advanced breast cancer, if no response is seen, dosage may be increased to 40 mg once daily.

Primary reduction of breast cancer risk

The recommended maximum dose is 20 mg daily for 5 years. There are insufficient data to support a higher dose or longer period of use.

An assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer risk is essential. Validated algorithms are available that calculate breast cancer risk based on features such as age, family history, genetic factors, reproductive factors, and history of breast disease.

NOLVADEX reduces, but does not eliminate, the risk of breast cancer. In clinical trials, NOLVADEX decreased the incidence of oestrogen receptor-positive tumours, but did not alter the incidence of oestrogen receptor-negative tumours. The use of NOLVADEX should be as part of a program including regular breast surveillance tailored to the individual woman, taking into account her risk of breast cancer.

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

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

* Not marketed

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of TGA Approval 4th April 2016

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