1. NAME OF THE MEDICINAL PRODUCT

Nolvadex

Nolvadex D

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nolvadex
Tamoxifen Citrate Ph. Eur. 15.2 mg (equivalent to 10 mg tamoxifen).

Nolvadex D
Tamoxifen Citrate Ph. Eur. 30.4 mg (equivalent to 20 mg tamoxifen).

Excipient with known effect: Lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nolvadex is indicated for:
1. The treatment of breast cancer.
2. The treatment of anovulatory infertility.
3. The primary prevention of breast cancer in women at moderate or high risk (see section 5.1).

Women aged less than 30 years old were excluded from primary prevention trials so the efficacy and safety of tamoxifen treatment in these younger women is unknown.

4.2 Posology and method of administration

Posology

1. Breast Cancer

Adults

The recommended daily dose of tamoxifen is normally 20 mg. No additional benefit, in terms of delayed recurrence or improved survival in patients, has been demonstrated with higher doses. Substantive evidence supporting the use of treatment with 30-40 mg per day is not available, although these doses have been used in some patients with advanced disease.

Elderly people
Similar dosing regimens of Nolvadex have been used in the elderly with breast cancer and in some of these patients it has been used as sole therapy.

2. Anovulatory Infertility
Before commencing any course of treatment, whether initial or subsequent, the possibility of pregnancy must be excluded. In women who are menstruating regularly, but with anovular cycles, the initial course of treatment consists of 20 mg given daily on the second, third, fourth and fifth days of the menstrual cycle. If unsatisfactory basal temperature records or poor pre-ovulatory cervical mucus indicate that this initial course of treatment has been unsuccessful, further courses may be given during subsequent menstrual periods, increasing the dosage to 40 mg and then to 80 mg daily.

In women who are not menstruating regularly, the initial course may begin on any day. If no signs of ovulation are demonstrable, then a subsequent course of treatment may start 45 days later, with dosage increased as above. If a patient responds with menstruation, then the next course of treatment is commenced on the second day of the cycle.

3. Primary prevention of breast cancer

Nolvadex treatment for the primary prevention of breast cancer should only be initiated by a medical practitioner experienced in prescribing for this indication, and as part of a shared care pathway arrangement, with appropriate patient identification, management and follow up.

The recommended dose is 20 mg daily for 5 years for those women at moderate or high risk. There are insufficient data to support a higher dose or longer period of use.

Before commencing treatment, an assessment of the potential benefits and risks is essential, including calculating a patient's risk of developing breast cancer according to local guidelines and risk assessment tools. 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.

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.

Paediatric population
The use of Nolvadex is not recommended in children. The safety and efficacy of Nolvadex in children has not yet been established (see sections 5.1 and 5.2).

Method of administration
For administration by the oral route.

4.3 Contraindications

General contraindications (all indications)
Nolvadex should not be used in the following:

- Pregnancy. Premenopausal patients must be carefully examined before treatment for all indications to exclude the possibility of pregnancy (see also section 4.6).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concurrent anastrozole therapy (see section 4.5).

Treatment for infertility
Nolvadex should not be used in:

- Patients with a personal or family history of confirmed idiopathic venous thromboembolic events or a known genetic defect.

Primary prevention of breast cancer
Nolvadex should not be used in:

- Women with a history of deep vein thrombosis or pulmonary embolus.
- Women who require concomitant coumarin-type anticoagulant therapy (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

The warnings and precautions for use are different depending on the indication being treated. The specific warnings and precautions for the primary prevention of breast cancer can be found at the end of the section.

Menstruation is suppressed in a proportion of premenopausal women receiving Nolvadex for the treatment of breast cancer.

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 underlying mechanism is unknown but may be related to the oestrogen-like effect of Nolvadex.

There are several factors that influence the risk of developing endometrial cancer, with the majority of risk factors affecting oestrogen levels. Therefore, Nolvadex treatment may increase the incidence of endometrial cancer. In addition, other risk

factors include obesity, nulliparity, diabetes mellitus, polycystic ovary syndrome and oestrogen-only HRT. There is also the general risk for endometrial cancer with increasing age. Any patient receiving or having previously received Nolvadex who report abnormal gynaecological symptoms, especially non-menstrual vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

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.

Venous thromboembolism

- A 2–3-fold increase in the risk for VTE has been demonstrated in healthy tamoxifen-treated women (see section 4.8).

- In patients with *breast cancer*, prescribers should obtain careful histories with respect to the patient's personal and family history of VTE. 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 (cross-reference section 4.5)

- 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. In patients with *breast cancer*, this risk is also increased by concomitant chemotherapy (see section 4.5). Long-term anticoagulant prophylaxis may be justified for some patients with *breast cancer* who have multiple risk factors for VTE.

- Surgery and immobility: For patients being treated for *infertility*, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and re-started only when the patient is fully mobile. For patients with *breast cancer*, 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. In patients being treated for *infertility*, tamoxifen should not be re-started unless there is a compelling alternative explanation for their thrombotic event. In patients receiving

tamoxifen for *breast cancer*, the decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients with *breast cancer*, the continued use of tamoxifen with prophylactic anticoagulation may be justified.

- *All* patients should be advised to contact their doctors immediately if they become aware of any symptoms of VTE.

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

In an uncontrolled trial in 28 girls aged 2–10 years with McCune Albright Syndrome (MAS), who received 20 mg 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 (see section 5.1).

In the literature it has been shown that CYP2D6 poor metabolisers have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen (see section 5.2).

Concomitant medications that inhibit CYP2D6 may lead to reduced concentrations of the active metabolite endoxifen. Therefore, potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided during tamoxifen treatment (see sections 4.5 and 5.2).

Nolvadex contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Radiation recall has been reported very rarely in patients on Nolvadex who have received prior radiotherapy. The reaction is usually reversible upon temporary cessation of therapy and re-challenge may result in a milder reaction. Treatment with Nolvadex was continued in most cases.

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. Non-gynaecological conditions such as cataracts were also increased (see section 4.8). 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 sections 4.4, 4.8 and 5.1).

In the primary prevention studies, due to the limited number of patients with a confirmed BRCA mutation there is uncertainty about the absolute benefit in these patients treated with tamoxifen for primary prevention of breast cancer.

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.

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 prevention trials, in contrast to women aged 50 years or older, 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.

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 sections 4.3 and 4.5). 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 6 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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

When Nolvadex is used in combination with cytotoxic agents for the treatment of breast cancer, there is increased risk of thromboembolic events occurring. (See also sections 4.4 and 4.8). Because of this increase in risk of VTE, thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy.

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

As Nolvadex is metabolised by cytochrome P450 3A4, care is required when co-administering with drugs, such as rifampicin, known to induce this enzyme as tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen), has been reported in the literature.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65-75% reduction in plasma levels of one of the more active forms of the drug, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see sections 4.4 and 5.2).

Primary prevention of breast cancer risk

In women receiving tamoxifen for the primary prevention of breast cancer, the use of coumarin type anticoagulants is contraindicated (see sections 4.3 and 4.4).

There is some evidence that hormone replacement therapy may reduce the effectiveness of tamoxifen, and the concomitant use of tamoxifen and oral hormonal contraceptives is not recommended. Therefore, the use of hormone replacement therapy or oral hormonal contraceptives to manage tamoxifen side effects is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women should be advised not to become pregnant whilst taking Nolvadex and should use barrier or other adequate 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.

Pregnancy
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 estradiol, ethinylestradiol, 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.

Breast-feeding
It is not known if Nolvadex is excreted in human milk and therefore the drug is not recommended during breast-feeding. The decision either to discontinue nursing or discontinue Nolvadex should take into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Nolvadex is unlikely to impair the ability of patients to drive or operate machinery. However, fatigue has been reported with the use of Nolvadex and caution should be observed when driving or using machinery while such symptoms persist.

4.8 Undesirable effects

Tabulated list of adverse reactions
The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Unless specified, the following frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9366

postmenopausal women patients with operable breast cancer treated for 5 years and unless specified, no account was taken of the frequency within the comparative treatment group or whether the investigator considered it to be related to study medication. The safety findings in the breast cancer prevention trials appeared consistent overall with the established safety profile of tamoxifen.

Table 1 Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency.

SOC	**Frequency**	**Adverse Drug Reaction**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Uterine fibroids
	Uncommon	Endometrial cancer
	Rare	Uterine Sarcoma (mostly malignant mixed Mullerian tumours)[a] Tumour Flare[a]
Blood and lymphatic system disorders	Common	Anaemia
	Uncommon	Thrombocytopenia Leukopenia
	Rare	Neutropenia Agranulocytosis
Immune system disorders	Common	Hypersensitivity reactions
Metabolism and nutrition disorders	Very common	Fluid retention
	Uncommon	Hypercalcaemia (in patients with bony metastases)
Nervous system disorders	Common	Ischaemic cerebrovascular events Headache Light headedness Sensory disturbances (including paraesthesia and dysgeusia)
	Rare	Optic neuritis
Eye disorders	Common	Cataracts Retinopathy
	Uncommon	Visual disturbances
	Rare	Corneal changes Optic neuropathy[a]
Vascular disorders	Very Common	Hot flushes
	Common	Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial pneumonitis
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea Constipation

	Uncommon	Pancreatitis
Hepatobiliary disorders	Common	Changes in liver enzymes Fatty liver
	Uncommon	Cirrhosis of the liver
	Rare	Hepatitis Cholestasis[a] Hepatic failure[a] Hepatocellular injury[a] Hepatic necrosis[a]
Skin and subcutaneous tissue disorders	Very common	Skin Rash
	Common	Alopecia
	Rare	Angioedema Steven-Johnsons syndrome[a] Cutaneous vasculitis[a] Bullous pemphigoid[a] Erythema multiforme[a]
	Very rare	Cutaneous lupus erythematosus[b]
Musculoskeletal and connective tissue disorders	Common	Leg cramp Myalgia
Reproductive system and breast disorders	Very common	Vaginal bleeding Vaginal discharge
	Common	Pruritus valvae Endometrial changes (including hyperplasia and polyps)
	Rare	Endometriosis[a] Cystic ovarian swelling[a] Vaginal polyps
Congenital, familial and genetic disorders	Very rare	Porphyria cutanea tarda[b]
General disorders and administration site conditions	Very common	Fatigue
Investigations	Common	Elevated triglycerides
Injury, poisoning and procedural complications	Very rare	Radiation Recall[b]

[a] This adverse drug reaction was not reported in the tamoxifen arm (n= 3094) of the above study; however, it has been reported in other trials or from other sources. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size e.g. 3094). This is calculated as 3/3094 which equates to a frequency category of 'rare'.

[b] The event was not observed in other major clinical studies. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size of 13,357 patients in the major clinical studies). This is calculated as 3/13,357 which equates to a frequency category of 'very rare'.

Side effects can be classified as either due to the pharmacological action of the drug, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae and tumour flare, or as more general side effects, e.g. gastrointestinal intolerance, headache, light-headedness and occasionally, fluid retention and alopecia.

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.

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

Uncommonly, patients with bony metastases have developed hypercalcaemia on initiation of therapy.

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

Cases of optic neuropathy and optic neuritis have been 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.

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.
Falls in platelet count, usually to 80,000 to 90,000 per cu mm but occasionally lower, have been reported in patients taking tamoxifen for breast cancer.

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.

There is evidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism, occurring commonly during tamoxifen therapy (see sections 4.3, 4.4 and 4.5). When Nolvadex is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

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

Uncommonly, cases of interstitial pneumonitis have been reported.

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.

Cystic ovarian swellings have rarely been observed in women receiving Nolvadex.

Vaginal polyps have rarely been observed in women receiving Nolvadex.

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

Porphyria cutanea tarda has been observed very-rarely 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.

Uncommonly incidences of endometrial cancer and rare instances of uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with Nolvadex treatment.

Primary prevention 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.

In the primary prevention trials 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.

Women under 50 years old

A meta-analysis of risk reduction trials stratified by age 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 years 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<00001); endometrial polyps (130 v 65, p<0,0001); ovarian cysts (101 v 42, p<00001); hysteroscopy (228 v 138, P<0,0001); pelvic ultrasound (209 v 132, p<00001); dilation and curettage (178 v 94, p<00001); hysterectomy (154 v 104, p=0002) and oophorectomy (103 v 67, p=0006).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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 (100–200 times recommended daily 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-estrogens. ATC code: L02BA01.

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. 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 10–20%. Tamoxifen does not adversely affect bone mineral density in postmenopausal women.

An uncontrolled trial was undertaken in a heterogenous group of 28 girls aged 2 to 10 years with McCune Albright Syndrome (MAS), who received 20 mg once a day for up to 12 months duration. Among the patients who reported vaginal bleeding during the pre-study period, 62% (13 out of 21 patients) reported no bleeding for a 6-month period and 33% (7 out of 21 patients) reported no vaginal bleeding for the duration of the trial. 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 (see section 4.4). There are no long-term safety data in children. In particular, the long-term effects of tamoxifen on growth, puberty and general development have not been studied.

CYP2D6 polymorphism status may be associated with variability in clinical response to tamoxifen. The poor metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of CYP2D6 poor metabolisers have not been fully elucidated (see sections 4.4, 4.5 and 5.2)

CYP2D6 genotype
Available clinical data suggest that patients who are homozygote for non-functional CYP2D6 alleles, may experience reduced effect of tamoxifen in the treatment of breast cancer.

The available studies have mainly been performed in postmenopausal women (see sections 4.4 and 5.2).

Primary reduction of breast cancer risk
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.

The breast cancer primary risk reduction trials include the International Breast Cancer Intervention Study (IBIS-1), the National Surgical Adjuvant Breast and Bowel Project PI 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-1and NSABP P1) or 8 years (Royal Marsden) and followed for up to 20 years.

The IBIS-1, NSABP PI, and Royal Marsden trials all defined breast cancer risk differently, and recruited women with both moderate or high lifetime risk: IBIS-1 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-1).

The majority of women in all trials were aged 59 years or below. NSABP PI 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 premenopausa1 (46% in IBIS-1 and 65% in Royal Marsden) or younger than 50 years old (37% NSABP P1).

A summary of the key entry criteria for each of the trials are shown in Table 2.

Table 2 Summary of Key Criteria Used to Select Patients in Each of the Main Studies

Study	**Key Entry Criteria**
IBIS 1	Aged 35-70 years No previous invasive cancer (except non-melanoma skin cancer) Relative risk of developing breast cancer: • At least two-fold in women aged 45-70 • At least four- fold in women aged 40-44 • At least ten-fold in women aged 35-39 Calculated using a specifically designed model based on family history and standard risk factors
NSABP P1	Aged >35 years No clinical evidence of breast cancer 5-year predicted risk >1.66% of developing breast cancer based on the Gail model, or a history of LCIS or atypical hyperplasia based on a multivariable logistic regression model
STAR	Aged >35 years 5 yr predicted risk of >1.66% of developing breast cancer based on Gail model
Marsden	Aged 30 - 70 years old

	No clinical evidence of breast cancer Increased risk of developing breast cancer based on family history.

Efficacy results from the trials are shown in Table 3, which 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 3 Summary of Key Efficacy and Safety Results from the Primary Risk Reduction Trials

	Cuzick meta-analysis[a]		**IBIS-1[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**
Efficacy	**HR (95% CI)**		**HR (95% CI)**		**RR (95% CI)**		**HR (95% CI)**	
All breast cancer	431 (3.0%)	634 (4.5%)	251 (7.0%)	350 (9.8%)	205 (3.1%)	343 (5.2%)	96 (7.7%)	113 (9.1%)
	0.67 (0.59-0.76)		0.71 (0.60-0.83)		NR		0.84 (0.64-1.10)	
Invasive breast cancer	NR		214 (6.0%)	289 (8.1%)	145 (2.2%)	250 (3.8%)	82 (6.6%)	104 (8.4%)
			0.73 (0.61-0.87)		0.57 (0.46-0.70)		0.78 (0.58-1.04)	
Non-invasive cancers	77 (0.5%)	112 (0.8%)	35 (1.0%)	53 (1.5%)	60 (0.9%)	93 (1.4%)	14 (1.1%)	9 (0.7%)
	0.72 (0.57-0.92)		0.65 (0.43-1.00)		0.63 (0.45-0.89)		NR	
Oestrogen receptor-positive cancers	219 (1.5%)	396 (2.8%)	160 (4.5%)	238 (6.7%)	70 (1.1%)	182 (2.8%)	53 (4.2%)	86 (7.0%)
	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 (0.8%)	103 (0.7%)	50 (1.4%)	47 (1.3%)	56 (0.8%)	42 (0.6%)	24 (1.9%)	17 (1.4%)
	1.13 (0.86-1.49)		1.05 (0.71-1.57)		1.31 (0.86-2.01)		1.4 (0.7-2.6)	
All cause mortality	1038 (2.3%*)	1050 (2.5%*)	182 (5.1%)	166 (4.6%)	126 (1.9%)	114 (1.7%)	54 (4.3%)	54 (4.3%)
	0·98* (0·90–1·06)		OR 1·10 (0·88–1·37)		RR 1.10 (0.85-1.43)		0.99 (0.68-1.44)	
Breast cancer mortality	30 (0.07%*)	29 (0.07%*)	31 (0.9%)	26 (1.0%)	12 (0.2%)	11 (0.2%)	12 (1.0%)	9 (0.7%)
	1.03* (0.55–1.92)		OR 1.19 (0.68–2.10)		NR		NR	
Safety	**Events OR or RR (95% CI)**							
Endometrial cancer	67 (0.5%)	31 (0.2%)	29 (0.8%)	20 (0.6%)	53 (0.8%)	17 (0.3%)	13 (1.0%)	5 (0.4%)
	OR 2.18 (95%CI 1.39-3.42)		OR 1.45 (95%CI 0.79-2.71)		RR 3.28 (95%CI 1.87-6.03)		NR	
Other cancers	787 (1.8%)	799 (1.9%)	322 (9.0%)	295 (8.3%)	NR		64 (5.1%)	70 (5.6%)
	OR 0.98* (95%CI 0.89-1.08)		NR				NR	
Venousthromboemblism (DVT,PE)	131 (0.9%)	82 (0.6%)	104 (2.9%)	62 (1.7%)	DVT 49 (0.7%) PE 28 (0.4%)	DVT 34 (0.5%) PE 13 (0.2%)	8 (0.6%)	3 (0.2%)

	OR 1.60 (95%CI 1.21-2.12)		OR 1.70 (95%CI 1.22-2.37)		DVT RR 1.44 (95%CI 0.91-2.30) PE RR 2.15 (95%CI 1.08-4.51)		NR	
Stroke	NR		30 (0.8%)	28 (0.8%)	71 (1.1%)	50 (0.8%)	7 (0.6%)	9 (0.7%)
			OR 1.07 (95%CI 0.62-1.86)		RR 1.42 (95%CI 0.97-2.08)		NR	
Fractures	731 (5.2%)	791 (5.6%)	240 (6.7%)	235 (6.6%)	80 (1.2%)	116 (1.8%)	19 (1.5%)	22 (1.8%)
	OR 0.92 (95%CI 0.83-1.02)		RR 1.02** (95%CI 0.86-1.21)		RR 0.68 (95%CI 0.51-0.92)		NR	

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = nonsignificant, 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 prevention 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
*This result is for all 9 studies included in the meta- analysis not just the tamoxifen studies, as it is not reported for just the tamoxifen studies. There was no heterogeneity between the studies for this category
** This result is after 8 years median follow up in the IBIS- 1 study, as not all adverse events continued to be recorded after this as no events were anticipated to occur more than 5 years after completion of treatment.

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-1 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. Therefore, the concomitant use of tamoxifen and hormone replacement therapy is not recommended for primary prevention of breast cancer.

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-1 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-1 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% CI0.33-0.73).

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.

5.2 Pharmacokinetic properties

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4–7 hours. Steady state concentrations (about 300 ng/ml) are achieved after four weeks treatment with 40 mg daily. The drug 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 drug itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

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.

Tamoxifen is metabolised mainly via CYP3A4 to N-desmethyl-tamoxifen, which is further metabolised by CYP2D6 to another active metabolite endoxifen. In patients who lack the enzyme CYP2D6 endoxifen concentrations are approximately 75% lower than in patients with normal CYP2D6 activity. Administration of strong CYP2D6 inhibitors reduces endoxifen circulating levels to a similar extent.

5.3 Preclinical safety data

Tamoxifen was not mutagenic in a range of *in vitro* and *in vivo* mutagenicity tests. Tamoxifen was genotoxic in some *in vitro* 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.

Tamoxifen is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose Sodium USNF
Gelatin Ph. Eur.
Lactose Ph. Eur.
Macrogol 300 B.P.
Magnesium Stearate Ph. Eur.
Maize Starch Ph. Eur.
Methylhydroxypropylcellulose Ph. Eur.
Titanium Dioxide Ph. Eur. (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Aluminium blister pack containing 30 or 250 tablets.
HDPE bottles containing 30 or 250 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
600 Capability Green,
Luton, LU1 3LU, UK.

8. MARKETING AUTHORISATION NUMBER(S)

Nolvadex: PL 17901/0033

Nolvadex D: PL 17901/0034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th June 2000

Date of latest renewal: 30th April 2008

10. DATE OF REVISION OF THE TEXT

05th April 2018