Nolvadex and Nolvadex-D
tamoxifen citrate
Tablets

Qualitative and quantitative composition
Nolvadex contains Tamoxifen Citrate Ph. Eur. 15.2 mg (equivalent to 10 mg of tamoxifen).
Nolvadex-D contains Tamoxifen Citrate Ph. Eur. 30.4 mg (equivalent to 20 mg of tamoxifen).

Pharmaceutical Form
Tablet.

Therapeutic indication
Nolvadex is indicated for the treatment of breast cancer.

Posology and method of administration
Route of administration: Oral.

Adults (including elderly): The dosage range is 20 to 40 mg daily, given either in divided doses twice daily or as a single dose once daily.

Use in children
The use of Nolvadex is not recommended in children, as safety and efficacy have not been established (see Pharmacodynamic and Pharmacokinetics properties).

Contraindications
Pregnancy: Nolvadex must not be given during pregnancy. Premenopausal patients must be carefully examined before treatment to exclude the possibility of pregnancy (see also Pregnancy and Lactation).

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

Special warnings and precautions for use
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. Any patient receiving or having previously received Nolvadex, who report abnormal gynaecological symptoms, especially 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 Undesirable effects).

- 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 (see Interaction with other medicinal products and other forms of interaction).

- 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. This risk is also increased by concomitant chemotherapy (see Interaction with other medicinal products and other forms of interaction). Long-term anticoagulant prophylaxis may be justified for some patients who have multiple risk factors for VTE.

- Surgery and immobility: 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. The decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients, 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 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 Pharmacodynamic properties).

Interactions 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, careful monitoring of the patient is recommended.

When Nolvadex is used in combination with cytotoxic agents, for the treatment of breast cancer, there is an increased risk of thromboembolic events occurring (see Special warnings and precautions for use and Undesirable effects). 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 an aromatase inhibitor 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. The relevance of this to clinical practice is not known.

Pregnancy and lactation
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 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.

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

Effects on ability to drive and use machines
There is no evidence that Nolvadex results in impairment of these activities.

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

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

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.

A number of cases of visual disturbances including infrequent reports of corneal changes and retinopathy have been described in patients receiving Nolvadex . An increased incidence of cataracts has been reported 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.

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.

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.

There is evidence of an increased incidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen therapy (see Contraindications, Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction). When Nolvadex is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

Leg cramps have been reported commonly in patients receiving Nolvadex.

Very rarely, cases of interstitial pneumonitis have been reported.

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

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

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been associated with Nolvadex treatment.

Overdose
On theoretical grounds, 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 QT interval of the ECG.

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

Pharmacodynamic properties
Nolvadex (tamoxifen) is a non-steroidal, triphenylene-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.

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 Special warnings and precautions for use). 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.

Pharmacokinetic properties
After oral administration, Nolvadex 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.

Pre-clinical safety data relevant to the prescriber
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.

Tamoxifen is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the packet leaflet text.

List of excipients
Croscarmellose Sodium Ph. Eur.
Gelatin Ph. Eur.
Lactose Ph. Eur.
Macrogol 300 Ph. Eur.
Magnesium Stearate Ph. Eur.
Maize Starch Ph. Eur.
Hypromellose (Hydroxypropylmethylcellulose or Methylhydroxypropylcellulose) Ph. Eur.
Titanium Dioxide Ph. Eur**.** (E171)

Incompatibilities
None known

Shelf life
Please refer to expiry date on blister strip and carton.

Special precautions for storage
Do not store above 30^{o}C. Store in original container.

Pack size
Please refer to outer carton for pack size.

Instructions for use, handling and disposal
Use as directed by the prescriber.

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AstraZeneca UK Limited, Macclesfield, Cheshire, United Kingdom.