PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Nolvadex®-D

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg tamoxifen in the form of tamoxifen citrate (30,4 mg)

Contains sugar: 234 mg lactose monohydrate

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film- coated tablet

White to off-white, octagonal, biconvex film-coated tablets intagliated with NOLVADEX-D on one face and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOLVADEX-D is indicated for the treatment of breast cancer. The response rate is similar to that seen with either oestrogens or androgens.

4.2 Posology and method of administration

Adults (including elderly):

The dose range is 20 mg to 40 mg daily given either in divided doses twice daily or as a single dose once daily.

Children:

The use of NOLVADEX-D is not recommended in children, as safety and efficacy have not been established (see section 5.1).

4.3 Contraindications

NOLVADEX-D must not be administered during pregnancy (see section 4.6). Pre-menopausal patients must be carefully examined before commencing treatment to exclude the possibility of pregnancy.

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

4.4 Special warnings and precautions for use

When NOLVADEX-D is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect, with risk of bleeding may occur. Where such co-administration is initiated, reduction of anticoagulant dosage and careful monitoring of the patient is recommended.

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).

Menstruation is suppressed in a proportion of premenopausal women receiving NOLVADEX-D.

Rare cases of pancreatitis have been observed in association with NOLVADEX-D therapy, mostly in patients with pre-treatment elevated triglycerides.

Very rarely cases of interstitial pneumonitis have been reported.

Endometrial changes:

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with NOLVADEX-D treatment. The underlying mechanism is unknown, but may be related to the oestrogen-like effect of NOLVADEX-D. Any women receiving or having previously received NOLVADEX-D, who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated.

Exacerbation of hereditary angioedema:

In patients with hereditary angioedema NOLVADEX-D may induce or exacerbate symptoms of angioedema.

Secondary tumours:

A number of second primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials.

In animal studies high doses of NOLVADEX-D increases ALA synthase activity, although in man no reports of porphyric attacks have been associated with NOLVADEX-D.

In delayed microsurgical breast reconstruction NOLVADEX-D 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).

Contains lactose:

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take NOLVADEX-D.

4.5 Interaction with other medicines and other forms of interaction

When NOLVADEX-D is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such coadministration is initiated for the treatment of breast cancer, careful monitoring of the patient is recommended.

When NOLVADEX-D is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see section 4.8).

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 have been reported in the literature. The relevance of this to Clinical practice is not known.

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. Reduced efficacy of NOLVADEX-D has been reported with concomitant use of some selective serotonin reuptake inhibitor (SSRI) antidepressants such as paroxetine.
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).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women should be advised not to become pregnant whilst taking NOLVADEX-D and for 9 months following cessation of therapy and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal women 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-D or within nine months of cessation of therapy.

Pregnancy

NOLVADEX-D must not be administered during pregnancy. There have been reports of spontaneous abortions, birth defects and foetus death after women have taken NOLVADEX-D.

In rodent models of foetal reproductive tract development, NOLVADEX-D 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 1 000 risk of developing clear-cell carcinoma of the vagina or cervix.

Lactation

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

4.7 Effects on ability to drive and use machines

There is no evidence that NOLVADEX-D results in impairment of these activities.
However, fatigue has been reported with the use of NOLVADEX-D and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects

When side-effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dosage range) without loss of control of the disease. If side-effects do not respond to this measure, it may be necessary to stop the treatment.

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).

System Organ Class	**Frequency**	**Adverse Event**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Uterine fibroids
	Uncommon	Endometrial cancer
	Rare	Uterine Sarcoma (mostly malignant mixed Mullerian tumours), Tumour Flare

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	Weight gain, hypercalcaemia (in patients with bony metastases),
Psychiatric disorders	Very common	Depression
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
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	Gastrointestinal intolerance: vomiting, diarrhoea, constipation
	Uncommon	Pancreatitis
Hepatobiliary disorders	Common	Changes in liver enzymes, fatty liver
	Uncommon	Cirrhosis of the liver
	Rare	Hepatitis, cholestasis, hepatic failure, hepatocellular injury**,** hepatic necrosis
Skin and subcutaneous tissue disorders	Very common	Skin rash
	Common	Alopecia

	Rare	Angioedema, Steven-Johnsons syndrome**,** toxic epidermal necrolysis, cutaneous vasculitis, bullous pemphigoid**,** erythema multiforme
	Very rare	Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common	Leg cramp, myalgia
Reproductive system and breast disorders	Very common	Vaginal bleeding, vaginal discharge, menstrual suppression
	Common	Pruritus valvae, endometrial changes (including hyperplasia and polyps)
	Rare	Endometriosis, cystic ovarian swelling, vaginal polyps
Congenital, familial and genetic disorders	Very rare	Porphyria cutanea tarda
General disorders and administration site conditions	Very common	Fatigue
Investigations	Common	Elevated triglycerides
Injury, poisoning and procedural complications	Very rare	Radiation recall

Cases of exacerbation of angioedema have been reported in patients with hereditary angioedema receiving NOLVADEX-D.

4.9 Overdose

On theoretical grounds, overdosage would be expected to cause enhancement of the pharmacological side effects. Animal studies showed that extreme overdosage (100-200 times the recommended daily dose) may produce oestrogenic effects.

There have been reports in the literature that NOLVADEX-D given at several times the standard dose may be associated with prolongation of the QT interval of the ECG.

There is no specific antidote and treatment must be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action:

Tamoxifen is a non-steroidal, triphenylethylene-based medicine which displays a complex spectrum of oestrogen antagonist and oestrogen-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.

An uncontrolled trial was undertaken in a heterogeneous group of 28 girls aged 2 to 10 years with McCune Albright Syndrome (MAS), who received a 20 mg dose 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) 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 1 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.

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 4 weeks treatment with 40 mg daily. The medicine is highly protein bound to serum albumin (> 99%). Metabolism is by hydroxylation, demethylation and conjugation. Excretion occurs primarily via the faeces. An elimination half-life of approximately 7 days has been calculated for the medicine itself, whereas that for N-desmethyltamoxifen 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.

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* 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, gelatine, lactose monohydrate, macrogol 300, magnesium stearate, maize starch, methylhydroxypropylcellulose and titanium dioxide.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in original container. Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

The tablets are packed into PVC aluminium foil blister strips.

Blister packs of 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

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8 REGISTRATION NUMBER(S)

S/21.12/41

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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