Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nolvadex D 20 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of tamoxifen present as tamoxifen citrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from Spain:
Round, white film-coated tablet marked ‘Nolvadex 20’ on one side, plain on the other side.

Product imported from the United Kingdom:
Octagonal, white film-coated tablet marked ‘Nolvadex D’ on one face and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nolvadex is indicated in the palliative management of Breast Cancer.

4.2 Posology and method of administration

Route of administration: Oral

***Breast Cancer :Adults (Including elderly)* :** the dose range is 20 to 40mg daily, given either in divided doses twice daily or as a single dose once daily.

In early disease, it is currently recommended that treatment is given for not less than 5 years. The optimal duration of Nolvadex therapy remains to be determined.

Children: Not applicable

4.3 Contraindications

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 also section 4.6)

Nolvadex 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

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

An increased incidence of endometrial 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 patients receiving or having previously received 'Nolvadex', who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated.

Nonetheless, the possibility that 'Nolvadex' may affect the development of endometrial pathology, including neoplasia, should be kept in mind when designing treatment regimens.

Investigations in different in vivo and in vitro systems have shown that tamoxifen has a genotoxic potential following hepatic activation. 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.

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 section 4.5 and 5.2).

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

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, careful monitoring of the patient is recommended.

When 'Nolvadex' is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see also section 4.8).
The use of tamoxifen in combination with anastrozole 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 finding is not known.

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 section 4.4 and 5.2).

4.6 Fertility, 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 in 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 appraised 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.

4.7 Effects on ability to drive and use machines

There is no evidence that 'Nolvadex' results in impairment of these activities.

4.8 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 and pruritus vulvae, or as more general side effects, e.g. gastrointestinal intolerance, headache, tumour flare, light headedness, and occasionally, fluid retention and alopecia.
When such side effects 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.

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 only to 80,000 - 90,000 per cu mm but occasionally lower, have been reported in patients taking 'Nolvadex' for breast cancer.

A number of cases of visual disturbance including infrequent reports of corneal changes and retinopathy have been described in patients receiving 'Nolvadex' therapy. An increased incidence of cataracts has been reported in association with the administration of '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'.

Leucopoenia 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 increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during 'Nolvadex' therapy. When 'Nolvadex' is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring. 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 reported in association with Nolvadex treatment.

4.9 Overdose

On theoretical grounds, overdosage would be expected to cause enhancement of the anti-oestrogenic side effects mentioned above. Observations in animals show that extreme overdosage (100 - 200 times recommended daily dose) may produce oestrogenic effects.
There is no specific antidote to overdosage and treatment must be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: L02B A01

'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 women with oestrogen receptor positive/unknown breast tumours, adjuvant tamoxifen has been shown to significantly reduce recurrence of the disease and improve 10-year survival, achieving a significantly greater effect with five years treatment than with 1 or 2 years treatment. These benefits appear to be largely irrespective of age, menopausal status, tamoxifen dose and additional chemotherapy. However, clinical studies have also shown some benefit in oestrogen receptor negative tumours in patients both with early and advanced disease, which may indicate other mechanisms of action.
In the clinical situation, it is recognised that tamoxifen leads to reduction in levels of blood total cholesterol and low density lipoproteins in postmenopausal women of the order of 10 - 20 %. Additionally tamoxifen has been reported to lead to maintenance of bone mineral density 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 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) 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 casual 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)

<u>CYP2D6 genotype</u>
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)

5.2 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.

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

Investigations in different in-vivo and in-vitro systems have shown that tamoxifen has a genotoxic potential following hepatic activation. 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 (Section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Gelatin
Lactose Monohydrate
Macrogol 300
Magnesium stearate
Maize starch
Hypromellose
Titanium Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blisters in packs of 30 tablets contained in an overlabelled outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 MARKETING AUTHORISATION NUMBER

PPA 465/133/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th May 2004
Date of last authorisation: 7th May 2008

10 DATE OF REVISION OF THE TEXT

January 2011