Tamoxifen 20mg Tablets

PL 20395/0010

UKPAR

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TAMOXIFEN 20MG TABLETS

PL 20395/0010

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Tamoxifen 20mg Tablets (product licence number: PL 20395/0010). This medicine is available only by prescription.

Tamoxifen 20mg Tablets belong to a group of medicines called anti-oestrogens. Tamoxifen is used to treat breast cancer. It can also be used to treat infertility caused by failure to ovulate properly.

Tamoxifen 20mg Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
TAMOXIFEN 20MG TABLETS

PL 20395/0010

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Tamoxifen 20mg Tablets to Relonchem Limited on 30 September 2009.

This is an abridged application made under Article 10.1 of EC Directive 2001/83, as amended. The applicant claims that the proposed product is a generic version of Nolvadex 20 (PL 17901/0034) licensed to AstraZeneca UK Ltd in the UK on 11 June 2000 following a change of ownership. The original brandleader marketing authorisation (PL 00029/0155) was granted in 1982, hence, has been marketed in the EEA for more than 10 years.

Tamoxifen is an oestrogen-receptor antagonist. It is used in the adjuvant endocrine therapy of early breast cancer and also to stimulate ovulation in women with anovulatory infertility.

The basis of this application depends on the bioequivalence study comparing the applicant’s product with the corresponding strength of the brandleader, taken from the UK market.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Tamoxifen citrate
Tamoxifen citrate is (Z)-2-[4-(1,2-diphenylbut-1-enyl) phenoxy]ethylamine citrate

\[
\begin{align*}
\text{C}_{26}\text{H}_{29}\text{NO}, \text{C}_6\text{H}_8\text{O}_7 \\
\text{MW} = 563.6 \\
\text{CAS No:} \ 54965-24-1
\end{align*}
\]

Tamoxifen citrate is a white or almost white powder. It is slightly soluble in water and acetone but soluble in methanol.

An appropriate specification in line with the Ph Eur monograph has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Full specifications are provided for the packaging used to store the tamoxifen, these are satisfactory.

Appropriate stability data have been generated supporting a retest period of 5 years.

DRUG PRODUCT

Description and Composition of the Drug Product
The product is presented as white, round tablets. Other ingredients are calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, providone, magnesium stearate and colloidal anhydrous silica.
All excipients are controlled in line with the relevant Ph. Eur. monograph. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

The applicant has provided satisfactory certificates stating that neither the excipients nor the active substance contain substances of human or animal origin.

There were no novel excipients used and no overages.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches and the results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The finished product is packed in blister strips (20µm aluminium foil / 250µm PVC film dark green coloured) that are then put in a carton which will contain 30 tablets.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. Stability results are considered acceptable to demonstrate the compatibility of the product with the proposed packaging.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with the storage precautions “do not store above 25 °C” and “store in the original package” is appropriate.

Bioavailability and bioequivalence
See clinical assessment.

Essential similarity
Results of comparative dissolution tests of the applicant’s product versus the UK brand leader product Nolvadex have been provided. The proposed product was shown to have a comparative dissolution profile to the UK brandleader product.

Product literature
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive
2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Conclusions**
A marketing authorisation may be granted for this application.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.
CLINICAL ASSESSMENT

INDICATIONS
Tamoxifen 20mg Tablets are indicated for:
1. The treatment of breast cancer.
2. The treatment of anovulatory infertility.

POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration: ORAL

Breast cancer:
Adults
The recommended daily dose of tamoxifen is normally 20mg. 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 patients
Similar dosing regimens of Tamoxifen 20mg Tablets have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

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.

TOXICOLOGY
No toxicology data has been submitted or is required for this application. A toxicological Expert report has been submitted.

This report states that Tamoxifen is well tolerated overall but that over the past 5 years, a number of case reports and clinical trials have associated tamoxifen therapy with an increased incidence of endometrial carcinoma. It concludes that the potential carcinogenic effect of tamoxifen in humans has to be considered and WHO has formally assessed tamoxifen as a carcinogenic drug.

There is no strong association with the duration of therapy and the incidence of endometrial carcinoma, and tamoxifen is not associated with high-grade, poor
prognosis disease. The WHO Expert Committee has included again tamoxifen in the current list of ‘Model List of Essential Drugs’. Therefore, several authors conclude that the benefits of tamoxifen in lives saved exceed the incidence of endometrial carcinoma.

However, because of the fact that the optimal duration do adjuvant therapy is not known and furthermore, drug resistance with changes of receptor status as well as stimulation of tumour growth may occur, the long-term tamoxifen treatment should be limited to 5 years.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**
A bio-equivalence study has been submitted comparing the Tamoxifen 20mg Tablets with the equivalent dose of Nolvadex.

**Bio-equivalence Study**
This study investigated the pharmacokinetics, distribution and the relative bio-availability of tamoxifen in healthy volunteers. The study was an open label, fixed dose study with five different study groups.

Study Groups were given either 20mg of Nolvadex or 20mg Tamoxifen Tablets

There were 18 patients in each group which were studied in the fasting state.

The pharmacokinetics of Tamoxifen 20mg Tablets and N-desmethyltamoxifen was evaluated and comparisons made between Study Groups I and II and between Study groups III and IV.

**Results**
The study report includes information on the 20mg formulations only.

**Tamoxifen 20mg Tablets**
There were no statistical differences between the treatment groups. Thus, the two groups can be considered identical based on demographic criteria for age, weight, height and body surface area.

The statistical calculations for the bio-availability of tamoxifen and N-desmethyltamoxifen from the reference Nolvadex 20 mg and the applicant’ Tamoxifen 20mg Tablets are shown in Tables 1 and 2, below:

**Table 1:**
Mean Pharmacokinetic Parameters of Tamoxifen after a Single Oral Dose of 20mg Tamoxifen (Nolvadex® 20 or Tamoxifen 20mg Tablets)
### PHARMACOKINETIC NOLVADEX® 20

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>mean</th>
<th>SD</th>
<th>CV(%)</th>
<th>Min</th>
<th>Max</th>
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<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>18</td>
<td>31.0</td>
<td>8.8</td>
<td>28.4</td>
<td>18.8</td>
<td>56.9</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>18</td>
<td>5.28</td>
<td>0.83</td>
<td>15.7</td>
<td>3.00</td>
<td>6.00</td>
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<tr>
<td>AUC$_{0-1}$ (ng·h/ml)</td>
<td>18</td>
<td>2070</td>
<td>540</td>
<td>26.1</td>
<td>1230</td>
<td>3310</td>
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<tr>
<td>AUC$_{0-\infty}$ (ng·h/ml)</td>
<td>18</td>
<td>2250</td>
<td>570</td>
<td>25.3</td>
<td>1320</td>
<td>3510</td>
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<tr>
<td>$T_{1/2}$ (h)</td>
<td>18</td>
<td>126</td>
<td>27</td>
<td>21.4</td>
<td>63.3</td>
<td>180</td>
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### PHARMACOKINETIC TAMOXIFEN 20MG TABLETS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
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<th>SD</th>
<th>CV(%)</th>
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<td>$C_{\text{max}}$ (ng/ml)</td>
<td>18</td>
<td>30.7</td>
<td>6.3</td>
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<td>20.6</td>
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<td>$T_{\text{max}}$ (h)</td>
<td>18</td>
<td>5.31</td>
<td>1.30</td>
<td>24.5</td>
<td>2.50</td>
<td>8.00</td>
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<tr>
<td>AUC$_{0-1}$ (ng·h/ml)</td>
<td>18</td>
<td>2030</td>
<td>470</td>
<td>23.2</td>
<td>1040</td>
<td>3120</td>
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<tr>
<td>AUC$_{0-\infty}$ (ng·h/ml)</td>
<td>18</td>
<td>2240</td>
<td>560</td>
<td>25.0</td>
<td>1140</td>
<td>3830</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>18</td>
<td>138</td>
<td>33</td>
<td>23.9</td>
<td>69.7</td>
<td>217</td>
</tr>
</tbody>
</table>

Table 2:

Statistical Results of Testing Treatment with Tamoxifen 20mg Tablets against Treatment with Nolvadex® 20 Using Mean Square Error Term From two Treatment ANOVA

#### Results for tamoxifen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diff (%)</th>
<th>Stat</th>
<th>Power</th>
<th>90% sym Cl (%)</th>
<th>90% shortest Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>0.8</td>
<td>n.s.d.</td>
<td>0.916</td>
<td>8.40</td>
<td>89.4 to 99.1</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.6</td>
<td>n.s.d.</td>
<td>0.979</td>
<td>6.90</td>
<td>92.4 to 108.8</td>
</tr>
<tr>
<td>AUC$_{0-1}$ (ng·h/ml)</td>
<td>2.1</td>
<td>n.s.d.</td>
<td>0.919</td>
<td>9.70</td>
<td>88.1 to 107.7</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng·h/ml)</td>
<td>0.8</td>
<td>n.s.d.</td>
<td>0.906</td>
<td>8.50</td>
<td>89.2 to 109.2</td>
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<td>$T_{1/2}$ (h)</td>
<td>9.8</td>
<td>n.s.d.</td>
<td>0.928</td>
<td>17.2</td>
<td>100.2 to 119.4</td>
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</tbody>
</table>

#### Results for n-desmethyl tamoxifen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diff (%)</th>
<th>Stat</th>
<th>Power</th>
<th>90% sym Cl (%)</th>
<th>90% shortest Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>12.7</td>
<td>n.s.d.</td>
<td>0.433</td>
<td>26.9</td>
<td>69.0 to 105.7</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>19.5</td>
<td>n.s.d.</td>
<td>0.236</td>
<td>40.0</td>
<td>54.0 to 107.1</td>
</tr>
<tr>
<td>AUC$_{0-1}$ (ng·h/ml)</td>
<td>7.7</td>
<td>n.s.d.</td>
<td>0.865</td>
<td>16.0</td>
<td>97.0 to 118.5</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (ng·h/ml)</td>
<td>6.1</td>
<td>n.s.d.</td>
<td>0.719</td>
<td>16.1</td>
<td>93.2 to 119.1</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>8.5</td>
<td>n.s.d.</td>
<td>0.480</td>
<td>21.8</td>
<td>91.3 to 125.7</td>
</tr>
</tbody>
</table>

**Diff:** Observed difference between means as % of reference mean
Study Conclusions
The results demonstrate that Nolvadex 20 mg and the applicant’s tamoxifen formulation are bio-equivalent for tamoxifen. Bio-equivalence for the metabolite N-desmethyltamoxifen is also suggested by the results of this study.

EFFICACY
No clinical efficacy data is required for this application.

SAFETY
No clinical safety data is required for this application.

PRODUCT LITERATURE
All product literature is medically satisfactory.

DISCUSSION
The data presented demonstrates the bio-equivalence of the proposed product to the reference Nolvadex 20mg. With reference to the CPMP Note for Guidance on the Investigation of Bio-availability and Bioequivalence (CPMP/EWP/QWP/1401/98), the bioequivalence study seems well designed, conducted, analysed, and reported.

RECOMMENDATIONS
A marketing authorisation may be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Tamoxifen 20mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of tamoxifen is well established.
The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with tamoxifen. The risk benefit is therefore considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 27 June 2003</td>
</tr>
<tr>
<td>2</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality and clinical dossiers on 20 October 2004</td>
</tr>
<tr>
<td>3</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality and clinical dossiers on 3 March 2005</td>
</tr>
<tr>
<td>4</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 15 April 2005</td>
</tr>
<tr>
<td>5</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 19 December 2006</td>
</tr>
<tr>
<td>6</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 16 February 2007</td>
</tr>
<tr>
<td>7</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 16 April 2007</td>
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<tr>
<td>8</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 26 October 2007</td>
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<td>9</td>
<td>Following assessment of the response the MHRA requested further information relating to the clinical dossier on 26 June 2008</td>
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<td>10</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 17 August 2009</td>
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<tr>
<td>11</td>
<td>The application was determined on 2 September 2009</td>
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</table>
1 NAME OF THE MEDICINAL PRODUCT
Tamoxifen 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 tablet contains 30.4mg tamoxifen citrate (equivalent to 20mg tamoxifen).

3 PHARMACEUTICAL FORM
Tablets
Round, white, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Tamoxifen 20mg Tablets are indicated for:

3. The treatment of breast cancer.
4. The treatment of anovulatory infertility.

4.2 Posology and method of administration
Route of administration: ORAL

Breast cancer

Adults
The recommended daily dose of tamoxifen is normally 20mg. 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 patients
Similar dosing regimens of Tamoxifen 20mg Tablets have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

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.

4.3 Contraindications
Tamoxifen 20mg Tablets must not be given during pregnancy. Premenopausal patients must be carefully examined before treatment for breast cancer or infertility to exclude the possibility of pregnancy (see also Section 4.6).

Tamoxifen 20mg Tablets should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.

Treatment for infertility: Patients with a personal or family history of confirmed idiopathic venous thromboembolic events or a known genetic defect.

4.4 Special warnings and precautions for use
Menstruation is suppressed in a proportion of pre-menopausal women receiving Tamoxifen 20mg Tablets 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 Tamoxifen 20mg Tablets treatment. The underlying mechanism is unknown but may be related to the oestrogen-like effect properties of Tamoxifen 20mg Tablets. Any patient receiving or having previously received Tamoxifen 20mg Tablets 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 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 anti-coagulant 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 anti-coagulant treatment.

- If any patients with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. In patients being treated for infertility, tamoxifen should not be restarted 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.

4.5 Interaction with other medicinal products and other forms of interaction
When Tamoxifen 20mg Tablets are 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 Tamoxifen 20mg Tablets are 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.

As Tamoxifen 20mg Tablets are 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.
4.6 Pregnancy and lactation

Pregnancy
Tamoxifen 20mg Tablets 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 Tamoxifen 20mg Tablets, 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, ethynylestradiol, 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 Tamoxifen 10mg Tablets and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal 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 Tamoxifen 20mg Tablets or within two months of cessation of therapy.

Lactation
It is not known if Tamoxifen 20mg Tablets are excreted in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue Tamoxifen 20mg Tablets 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 Tamoxifen 20mg Tablets result 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, pruritus vulvae and tumour flare, or as more general side effects, e.g. gastro-intestinal 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 20mg/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 disturbance including reports of corneal changes and retinopathy have been described in patients receiving Tamoxifen 20mg Tablets. An increased incidence of cataracts has been reported in association with the administration of Tamoxifen 20mg Tablets.

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.

Cystic ovarian swellings have occasionally been observed in pre-menopausal women receiving Tamoxifen 20mg Tablets.

Leucopenia has been observed following the administration of Tamoxifen 20mg Tablets, sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe.

Cases of deep vein thrombosis and pulmonary embolism have been reported during Tamoxifen therapy (see sections 4.3, 4.4 and 4.5.). When Tamoxifen 20mg Tablets are used in combination with cytotoxic agents, there is an increased risk of thrombo-embolic events.

Very rarely, cases of interstitial pneumonitis have been reported.

Tamoxifen 20mg Tablets have 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 Tamoxifen 20mg Tablets.

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumour) has been reported in association with Tamoxifen 20mg Tablets treatment.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
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. However, clinical studies have shown some benefit in oestrogen receptor negative tumours which may indicate other mechanisms of action. 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 – 2- % Tamoxifen does not adversely affect bone mineral density.

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 40mg 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-desmethyaltamoxifen, the principal circulating metabolite, is 14 days.

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
Calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, providone, magnesium stearate, colloidal anhydrous silica.

6.2 Incompatibilities
None known.
6.3 **Shelf life**
Three years.

6.4 **Special precautions for storage**
Do not store above 25 °C. Store in the original package.

6.5 **Nature and contents of container**
Blister strips (20µm aluminium foil / 250µm PVC film dark green coloured)
Blister strips and leaflet in folding cartons (pack size: 30 tablets).

6.6 **Special precautions for disposal**
No special instructions.

7 **MARKETING AUTHORISATION HOLDER**
Relonchem Limited,
27 Old Gloucester Street,
London
WC1 3XX

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20395/0010

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
30/09/2009

10 **DATE OF REVISION OF THE TEXT**
30/09/2009
Tamoxifen 20mg Tablets

Package Leaflet: Information for the User

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others, it may harm them, even if their symptoms are the same as yours.
- If any side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
- What Tamoxifen 20mg Tablets are and what they are used for
- Before you take Tamoxifen 20mg Tablets
- Special precautions
- How to take Tamoxifen 20mg Tablets
- Possible side effects
- How to store Tamoxifen 20mg Tablets
- Further information

1. What Tamoxifen is and what it is used for

Tamoxifen belongs to a group of medicines known as anti-oestrogens. Tamoxifen is used to treat breast cancer. It can also be used to treat infertility caused by a failure to ovulate properly.

2. Before you take Tamoxifen 20mg Tablets

Do not take Tamoxifen 20mg Tablets if you
- are pregnant
- are breast-feeding
- are taking anticoagulant tablets?
- have ever had an allergic reaction to tamoxifen or to any of its ingredients.

Tamoxifen should not be taken by women who are pregnant or breast feeding.

Taking other medicines

Tamoxifen 20mg Tablets can interact with certain types of anticoagulant medicine and a drug called rifampicin (for tuberculosis). Please ask your doctor or pharmacist before you take other medicines at the same time or if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

3. Special Precautions

Pregnancy
You should not become pregnant when taking Tamoxifen 20mg Tablets. Please see your doctor for advice on what contraceptive precautions you should take, as some may be affected by tamoxifen. You should see your doctor immediately if you think you may have become pregnant after starting to take Tamoxifen 20mg Tablets.

Driving and using machines
There is no evidence to suggest that Tamoxifen 20mg tablets affect the ability to drive or use machines.

4. How to take Tamoxifen 20mg Tablets

Follow your doctor’s instructions about when and how to take your medicine. Also read the label. Your pharmacist can also help if you are not sure.

The usual dose to treat breast cancer is 20mg daily. The daily dose can either be taken as a single dose every day or a dose can be divided in two and taken in the morning and the evening.

The dosage for infertility depends on the menstrual cycle. In women who are having regular periods treatment usually begins by taking 20mg of tamoxifen daily on the second, third, fourth and fifth days of the menstrual cycle. If this is not successful, your doctor may increase the dosage on these days to 40mg or 80mg daily.

In women who are not having regular periods, the treatment can be started on any day.

If you forget to take a dose, take it as soon as you remember and then carry on as before.

If you take more Tamoxifen 20mg tablets than you should

If you (or someone else) swallow a lot of the tablets at the same time, or you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

5. Possible side effects

Like all medicines Tamoxifen 20mg Tablets can cause side effects, although not everybody gets them.

Occasionally, a few people can suffer from stomach or gut upsets, headaches, light-headedness, menstrual disturbances, hot flushes, genital itching, vaginal discharge or
bleeding, fluid retention, hypertriglyceridemia (increased levels of fat in your blood) sometimes with pancreatitis (pain or tenderness in your upper abdomen), skin rashes or itching or peeling skin, thinning of the hair, or inflammation of the lungs (which may present with the same symptoms as pneumonia, such as breathlessness and cough).

Other possible events are changes in vision or difficulty seeing properly as a result of cataracts or changes to the cornea or retina, an increased risk of blood clots, a tendency to bruise more easily, ovarian cysts or certain liver problems such as jaundice. Other possible events are effects on the endometrium (lining of the womb) which may also be seen as discomfort in the pelvis or as vaginal bleeding.

It is important that you tell your doctor immediately if you have any unusual vaginal bleeding, menstrual irregularities, vaginal discharge or discomfort in the pelvis such as pain or pressure when you are taking tamoxifen or any time afterwards. This is because a number of changes to the lining of the womb (the endometrium) may occur, some of which may be serious and could include cancer.

At the beginning of treatment for breast cancer, the symptoms of the disease can sometimes get worse, for example an increase in pain or an increase in the size of the affected tissue. In addition, if you get excessive nausea, vomiting or thirst, tell your doctor because this may mean that there are changes in the amount of calcium in your blood and your doctor may want to check this.

Do not be alarmed by this list of possible events. You may not have any of them.

If you get any other undesirable effects or if you think your medicine is causing any problems, tell your doctor or pharmacist

**STOP TAKING** Tamoxifen 20mg Tablets and contact your doctor immediately in any of the following situations:

- If you develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.
- If you develop swelling of the face, lips, tongue and/or throat which may cause difficulty swallowing.
- If you develop swelling of the hands, feet or ankles.
- If you develop urticaria ('hives')

### 6. How to Store Tamoxifen 20mg Tablets

Keep out of the reach and sight of children.

Do not store above 25°C. In order to protect from light, store in the original package.

Do not use after the expiry date shown on the carton and blister.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measure will help to protect the environment.

### 7. Further Information

**What Tamoxifen 20mg Tablets contain**

- The active substance (the ingredient which makes the medicine work) is tamoxifen (as citrate).
- The other inactive ingredients are calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate and colloidal anhydrous silica.

**What Tamoxifen 20mg Tablets look like and contents of the pack**

Tamoxifen 20mg Tablets are white, round tablets with a score line and ‘TN20’ embossed on one side and contain 20mg of tamoxifen.

Tamoxifen 20mg Tablets are available in Blister packs containing 30 tablets.

**Marketing Authorisation Holder and Manufacturer**

The Marketing Authorisation Holder is:
Relonchem Limited
27 Old Gloucester Street,
London WC1 JXX.

The Manufacturer is:
Heumann Pharma, Nuemberger Strasse 12, 90537 Feucht, Germany.

PL Number: 20395/0010

This Leaflet was approved in: XXX