Public Assessment Report

UK PAR

Tamoxifen 20 mg Tablets
(tamoxifen citrate)

UK Licence No: PL 33414/0154

Chelona Healthcare Limited
LAY SUMMARY

Tamoxifen 20 mg Tablets
(tamoxifen citrate)

This is a summary of the Public Assessment Report (PAR) for Tamoxifen 20 mg Tablets (PL 02142/0050). For ease of reading, Tamoxifen 20 mg Tablets may be referred to as ‘Tamoxifen’ in this lay summary. The lay summary explains how the application for Tamoxifen was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Tamoxifen Tablets.

For practical information about using Tamoxifen, patients should read the package leaflet or contact their doctor or pharmacist.

What is Tamoxifen and what is it used for?
Tamoxifen is a ‘generic’ medicines. This means that Tamoxifen is similar to a ‘reference medicine’ called Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK), which were first authorised in the UK in 1982.

This medicine is used to treat:
- breast cancer
- infertility in women caused by a failure to produce and release eggs (ovulate) properly
- it can also reduce the risk of developing breast cancer occurring in those women who have an increased likelihood of developing breast cancer (the patient’s risk). It is important that the patient’s healthcare professional calculates the patient’s risk of developing breast cancer and discusses the result with the patient before commencing treatment. There are a number of specific tools available to calculate breast cancer risk, based on information such as the patient’s age, family history, genetics, reproductive factors (e.g. age when periods started and stopped, had children or not, taken or taking hormonal replacement therapy and/or oral contraceptive pill) and history of breast disease.

Although the tools can estimate the patient’s risk, it does not mean the patient will get breast cancer, being at increased risk means the patient has a higher chance of developing breast cancer. If the patient’s health professional and patient are considering the patient using Tamoxifen for this indication, It is important for the patient to understand the benefits as well as the side effects of taking Tamoxifen as the patient does not currently have breast cancer and tamoxifen reduces, but does not stop the risk of developing breast cancer.

The patient should ask their doctor if not sure why they have been prescribed these tablets.

How does Tamoxifen work?
The active substance, tamoxifen (as tamoxifen citrate) belongs to a group of medicines known as ‘anti-oestrogens’. Oestrogen is a natural substance in your body known as a ‘sex-hormone’. Tamoxifen works by blocking the effects of oestrogen.

How is Tamoxifen used?
The pharmaceutical form for this medicine is tablet. The tablets should be swallowed whole. Tamoxifen Tablets may be taken as a single dose or in divided doses if appropriate.

Tamoxifen can only be obtained with a prescription.
Tamoxifen should always be taken exactly as advised by the patient’s doctor or pharmacist. The patient should check with the doctor or pharmacist if not sure. The patient’s doctor will advise him/her as to how much medicine to take.

Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Tamoxifen is not intended for use in children

**What benefits of Tamoxifen has been shown in studies?**
As Tamoxifen is generic medicine, studies in patients have been limited to tests to determine that Tamoxifen Tablets are bioequivalent to the reference medicine, Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Tamoxifen?**
Because Tamoxifen is a generic medicine and is bioequivalent to the reference medicine Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK), the possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Tamoxifen, see Section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why is Tamoxifen approved?**
It was concluded that, in accordance with EU requirements, Tamoxifen has been shown to have comparable quality and to be bioequivalent to Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK). Therefore, the view was that, as for Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK), the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Tamoxifen?**
A Risk Management Plan has been developed to ensure that Tamoxifen is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Tamoxifen, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Tamoxifen**
A Marketing Authorisation was granted in the UK to Chatfield Pharmaceuticals Limited on 14 March 2012.

Following the grant of a Change of Authorisation holder (CoA) procedure, the Marketing Authorisation were transferred to Chelona Healthcare Limited (PL 33414/0154) on 11 December 2014.

A variation to add the indication ‘primary prevention of breast cancer in women at moderate or high risk’ was granted on 11 July 2018.

The full PAR for Tamoxifen follows this summary.
For more information about treatment with Tamoxifen, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.
# SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Chatfield Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Tamoxifen 20 mg Tablets (PL 02142/0050) on 14 March 2012. The product is a prescription-only medicine indicated for the:
- treatment of breast cancer.
- treatment of anovulatory infertility.
- primary prevention of breast cancer in women at moderate or high risk

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.

This application was submitted under Article 10(1) of Directive 2001/83/EC (as amended), claiming to be a generic medicinal product of Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK), which were first authorised in the UK in 1982.

The active ingredient, tamoxifen (as tamoxifen citrate), belongs to the triphenylethylene class of compounds derived from the same stilbene nucleus as diethylstilbestrol; compounds of this class display a variety of oestrogenic and antioestrogenic activities. In primates, including humans, tamoxifen acts primarily as an oestrogen antagonist.

Tamoxifen is a competitive inhibitor of estradiol binding to the oestrogen receptor (ER). When bound to the ER, tamoxifen induces a change in the three-dimensional shape of the receptor, inhibiting its binding to the oestrogen-responsive element (ERE) on DNA. Under normal physiological conditions, oestrogen stimulation increases tumour cell production of transforming growth factor β (TGF-β), an autocrine inhibitor of tumour cell growth. By blocking these pathways, the net effect of tamoxifen treatment is to decrease the autocrine stimulation of breast cancer growth. In addition, tamoxifen decreases the local production of insulin-like growth factor 1 (IGF-1) by surrounding tissues; IGF-1 is a paracrine growth factor for the breast cancer cell.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support this application, comparing the test product Tamoxifen 20 mg Tablets (Chatfield Pharmaceuticals Limited, UK) with the reference product Nolvadex (ICI Pharma, Germany) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Tamoxifen 20 mg Tablets outweigh the risks and a Marketing Authorisation was granted.

Following the grant of a Change of Authorisation holder (CoA) procedure, the Marketing Authorisation were transferred to Chelona Healthcare Limited (PL 33414/0154) on 11 December 2014.
II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a round, white to off-white tablet with a break-line and “20” imprinted on one side. Each tablet contains 20 mg of tamoxifen (as citrate). Other ingredients consist of the pharmaceutical excipients calcium hydrogen phosphate, Povidone K25, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica and sodium starch glycollate, Type A. Appropriate justification for the inclusion of each excipient has been provided.

II.2 Drug Substance

INN: Tamoxifen citrate
Chemical Name: (Z)-2-[4-(1,2-diphenylbut-1-enyl) phenoxy]ethylamine citrate
Molecular Formula: C_{26}H_{29}NO, C_{6}H_{8}O_{7}
Structure

![Molecular structure of Tamoxifen citrate]

Molecular weight: 563.6
Appearance: A white or almost white crystalline powder, slightly soluble in water, soluble in methanol, slightly soluble in acetone.

Tamoxifen citrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance tamoxifen citrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product Nolvadex-D 20 mg tablets (AstraZeneca UK Limited, UK)

Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product and the reference product.
All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.
Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future commercial batches.

Control of Finished Product
The finished product specification is satisfactory. Test methods have been described and 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 tablets are packaged in dark green coloured polyvinylchloride/aluminium blisters. These are packed into cardboard cartons with patient information leaflet in pack sizes of 28, 30, 56, 60, 84, 90, 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 4 years has been proposed, with the storage conditions ‘Do not store above 25°C. Store in the original package’.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Conclusion
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of tamoxifen citrate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL OVERVIEW
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
IV. CLINICAL ASPECTS

IV.1 Introduction

Clinical Pharmacology

The clinical pharmacology of tamoxifen citrate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study:

A randomised, single-dose, open-label, parallel group study to compare the pharmacokinetics of the test product Tamoxifen 20 mg Tablets (Chatfield Pharmaceuticals, UK) versus the reference product Nolvadex (ICI Pharma, Germany) in healthy adult male subjects under fasting conditions.

The subjects were selected so that pairs with very similar demographic characteristics (‘twins’) were formed. The twin subjects were randomly allocated to either of the treatment groups. The subjects were given a single dose of the test or reference product with 200 ml of water after an overnight fast of at least 12 hours. Subjects remained fasted for six hours following study drug administration. Standardised meals were served 6 and 12 hours after dosing. Blood samples were collected before and up to 504 hours after each administration. The pharmacokinetic results are presented below for tamoxifen and the active metabolite N-desmethyltamoxifen:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (mean±SD, ratios and confidence intervals [CI]) of tamoxifen</th>
<th>Tamoxifen 20 mg (Test)</th>
<th>Nolvadex (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ng h/ml)</td>
<td>2030±470</td>
<td>2070±540</td>
<td>0.89</td>
<td>0.98-1.09</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng h/ml)</td>
<td>2240±560</td>
<td>2250±570</td>
<td>0.99</td>
<td>0.90-1.10</td>
</tr>
<tr>
<td>C\text{max} (ng/ml)</td>
<td>30.7±6.3</td>
<td>31.0±8.8</td>
<td>1.01</td>
<td>0.92-1.11</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C\text{max} maximum plasma concentration
SD= standard deviation
Ratios and 90% CI calculated from ln-transformed data

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (mean±SD, ratios and confidence intervals [CI]) of N-desmethyltamoxifen (active metabolite)</th>
<th>Tamoxifen 20 mg (Test)</th>
<th>Nolvadex (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
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<tbody>
<tr>
<td>AUC_{0-t} (ng h/ml)</td>
<td>2030±470</td>
<td>2070±540</td>
<td>1.10</td>
<td>1.00-1.22</td>
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<tr>
<td>AUC_{0-inf} (ng h/ml)</td>
<td>2240±560</td>
<td>2250±570</td>
<td>1.06</td>
<td>0.94-1.19</td>
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<tr>
<td>C\text{max} (ng/ml)</td>
<td>11.6±1.8</td>
<td>13.3±8.5</td>
<td>0.97</td>
<td>0.85-1.10</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C\text{max} maximum plasma concentration
SD= standard deviation
Ratios and 90% CI calculated from ln-transformed data

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80.00 to 125.00 % for AUC and \( C_{\text{max}} \) values. The 90 % confidence intervals of the test/reference ratio of geometric means for AUC_{0-t}, AUC_{0-inf} and C\text{max} lie within the acceptable limits. Thus, the data support the claim that the test product Tamoxifen 20 mg Tablets (Chatfield...
Pharmaceutical Limited, UK) is bioequivalent to the accepted reference product Nolvadex (ICI Pharma, Germany).

EFFICACY
The efficacy of tamoxifen citrate is well-known. No new efficacy data have been submitted and none are required for this type of application.

SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

CLINICAL OVERVIEW
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.

V. USER CONSULTATION
A 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, as amended. 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.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Tamoxifen 20 mg 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.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of tamoxifen citrate are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Tamoxifen 20 mg Tablets and an acceptable reference product under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of tamoxifen citrate is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

**BENEFIT/RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tamoxifen citrate is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.

**RECOMMENDATION**

The grant of a Marketing Authorisation is recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is presented below:
Chelonia Healthcare Ltd, 11 Boumpoulinas, Nicosia, P.C. 1060, Cyprus
Tamoxifen 20 mg Tablets

(tamoxifen citrate)

PL 33414/0154

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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| 12/06/2018     | Type IB          | 1. To update SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 to include the new indication ‘primary prevention of breast cancer in women at moderate or high risk’ recently approved for the brand leader Nolvadex D (PL 17901/0034, AstraZeneca).  
## Annex 1

<table>
<thead>
<tr>
<th>Our Reference:</th>
<th>PL 33414/0154, Application 0019</th>
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<tr>
<td>Product:</td>
<td>Tamoxifen 20 mg Tablets</td>
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<tr>
<td>Marketing Authorisation Holder:</td>
<td>Chelonia Healthcare Limited</td>
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<td>Active Ingredient(s):</td>
<td>Tamoxifen citrate</td>
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<th>National</th>
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<td>Type IB</td>
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<tr>
<td>Submission Complexity:</td>
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| EU Procedure Number (if applicable): |

### Reason:
1. To update SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 to include the new indication ‘primary prevention of breast cancer in women at moderate or high risk’ recently approved for the brand leader Nolvadex D (PL 17901/0034, AstraZeneca).
2. To submit an updated Risk Management Plan (RMP).

### Supporting Evidence
- Revised SmPC fragments
- Updated PIL
- Updated RMP

### Evaluation
The proposed changes to the SmPC and PIL are satisfactory.

An acceptable Risk Management Plan (RMP) has been submitted. Routine pharmacovigilance and routine risk minimisation activities are proposed for all safety concerns.

### Conclusion
The proposed changes to the SmPC and PIL are considered acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website.

The proposed changes to the RMP are acceptable. There are no differences from the reference product in terms of proposed uses, posology, strength or pharmaceutical form / formulation that would have any implications for safety.

### Decision – Approved on 11 July 2018