TAMOXIFEN 20 MG TABLETS
PL 02142/0050

UKPAR

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TAMOXIFEN 20 MG TABLETS
PL 02142/0050

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Chatfield Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Tamoxifen 20 mg Tablets (PL 02142/0050) on 14 March 2012. This medicine is only available on prescription from your doctor and is used to treat:

- breast cancer
- infertility in women caused by a failure to produce and release eggs (ovulate) properly.

Tamoxifen 20 mg Tablets contain the active ingredient, tamoxifen (as tamoxifen citrate), which 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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tamoxifen 20 mg Tablets outweigh the risks and a Marketing Authorisation was granted.
TAMOXIFEN 20 MG TABLETS
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SCIENTIFIC DISCUSSION

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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.
- anovulatory infertility.

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 $\beta$ (TGF-$\beta$), 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.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Tamoxifen citrate
Chemical Name: (Z)-2-[4-(1,2-diphenylbut-1-enyl) phenoxy]ethylamine citrate
Molecular Formula: \( C_{26}H_{29}NO_2C_6H_8O_7 \)
Structure

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.

DRUG PRODUCT

Other Ingredients
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.

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.

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 \textit{in-vitro} dissolution and impurity profiles have been provided for this product and the reference product.
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 leaflets 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.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

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.
MAA (Marketing Authorisation Application) Form
The MAA form is pharmaceutically satisfactory.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

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 EXPERT REPORT (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.
CLINICAL ASSESSMENT

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_{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_{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>
</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>C_{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_{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 $AUC_{0-t}$, $AUC_{0-\text{inf}}$ 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.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPC, PIL and labelling are satisfactory from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

**Clinical Expert Report (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.
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.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with current guidance.

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.
TAMOXIFEN 20 MG TABLETS
PL 02142/0050

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 15 April 2002.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 17 June 2002.


5 The application was determined and granted on 14 March 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Tamoxifen 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 20 mg tamoxifen (as citrate).
For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablets
Round, white to off-white tablets with the Chatfield logo on one side and a breakline and TAM20 imprinted on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Tamoxifen 20 mg Tablets are indicated for:
The treatment of breast cancer.
The treatment of anovulatory infertility.

4.2 Posology and method of administration
Tamoxifen 20 mg Tablets are for oral administration.
Breast cancer
Adults:
The recommended daily dose for tamoxifen is normally 20 mg. 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.

The elderly:
The adult dosage range has been used in elderly patients with breast cancer.

Anovulatory infertility
The possibility of pregnancy must be excluded before the commencement of treatment. In women with regular menstruation but anovular cycles, treatment should commence with 20 mg daily administered on the 2nd, 3rd, 4th and 5th days of the menstrual cycle. Should the initial course of treatment, as judged by basal temperature or pre-ovulatory cervical mucus, prove unsuccessful, further courses may be given during subsequent menstrual periods, increasing the dosage to 40 mg daily and then to 80 mg daily.

In women who are not menstruating regularly, the commencement of treatment may take place on any day. If this initial course is not successful then a further course may be initiated after an interval of 45 days with the dosage increased as above. If a patient responds with menstruation then the next course of treatment is started on the second day of the cycle.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Pregnancy and breast feeding (see Section 4.6).

4.4 Special warnings and precautions for use
Tamoxifen may be given to pre-menopausal women only after thorough examination has excluded the possibility of pregnancy.

An increased incidence of endometrial changes, including hyperplasia, polyps and cancer, has been reported in association with tamoxifen (see Undesirable Effects).

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.
Occasional cystic ovarian swellings may occur in premenopausal women. Hypercalcaemia can occasionally occur if bony metastases are present. There is an increased risk of thromboembolic events occurring when used with cytotoxics.

Tamoxifen is unsafe for use in acute porphyrias.

4.5 Interaction with other medicinal products and other forms of interaction
Tamoxifen increases the dopaminergic effect of bromocriptine.
Aminoglutethimide reduces the plasma concentration of tamoxifen.
Concurrent use of oestrogens may interfere with tamoxifen’s therapeutic effect.
Tamoxifen may potentiate the anti-coagulant action of warfarin if these drugs are used concomitantly. Patients taking coumarin-type anti-coagulants will require close monitoring on the introduction or withdrawal of tamoxifen.

As tamoxifen is metabolised by cytochrome P450 3A4, care is required when coadministering with drugs, such as rifampicin, known to induce this enzyme, because tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown.

4.6 Fertility, pregnancy and lactation
Tamoxifen 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, 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 and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal patients must be carefully examined before treatment to exclude pregnancy. Women should be informed of the potential risks to the foetus, should they become pregnant whilst taking tamoxifen or within two months of cessation of therapy.

It is not known if tamoxifen is excreted in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue tamoxifen 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 results in impairment of these activities.

4.8 Undesirable effects
Side effects can occasionally be controlled by reducing the dosage (to not less than 20 mg/day) without loss of therapeutic effect. If side-effects persist, it may be necessary to discontinue treatment.

The following side-effects have been reported: hot flushes, rashes, dry skin, pruritus vulvae, vaginal discharge or bleeding, uterine fibroids, dizziness, confusion, headache, light-headedness, depression, muscle cramps, fatigue, fluid retention, alopecia, and gastrointestinal disturbances including nausea, vomiting and anorexia.
On rare occasions Stevens-Johnson syndrome, erythema multiforme, bullous pemphigoid and hypersensitivity reactions including angioedema have been reported.
Occasional tumour flare and pain have been reported. In some patients with bony metastases, hypercalcaemia has been observed at the start of treatment.

The incidence of thromboembolic events may increase. These include deep vein thrombosis and pulmonary embolism.

Elevation of serum triglyceride levels have been reported and pancreatitis has occurred. Leucopenia has been reported sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has also been reported on rare occasions. Decreased platelet counts - usually to 80,000-90,000 per mm$^3$ but occasionally lower - have been reported in patients taking tamoxifen for breast cancer.

Rarely blurred vision, loss of visual acuity, retinopathy, corneal opacities and cataracts have been reported.

Menstruation is suppressed in a number of pre-menopausal women receiving tamoxifen. Cystic ovarian swellings have occasionally been observed.

Endometrial hyperplasia, endometriosis, endometrial polyps, an increased incidence of endometrial carcinoma and uterine sarcoma (mostly malignant mixed Mullerian tumours) have been reported in association with tamoxifen treatment. Abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and symptoms such as pelvic pain or pressure in patients receiving (or who have previously received) tamoxifen should be promptly investigated.

Tamoxifen has been associated with changes in liver enzyme levels and rarely with more severe liver abnormalities including fatty liver, cholestasis, and hepatitis. Very rarely, cases of interstitial pneumonitis have been reported.

4.9 Overdose
Overdose in humans has not been reported. On theoretical grounds, an overdose would be expected to cause an enhancement of the anti-oestrogenic effects as described above. In animals, extremely high doses (over 100 times the recommended daily dose) have caused oestrogenic effects. There is no special antidote to overdosage and treatment should therefore be symptomatic.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Tamoxifen is a non-steroidal anti-oestrogen, ATC code: L02B A. It binds to oestrogen receptors preventing the stimulating effects of oestrogen on nucleic acid synthesis. The metabolites of tamoxifen are also anti-oestogens.

5.2 Pharmacokinetic properties
Maximum plasma levels of tamoxifen occur at 4-7 hours after administration. Steady-state levels of approximately 300 mg/l are achieved after 4 weeks’ treatment with 20 mg daily. The elimination half-life is about 7 days but may be up to 14 days for the principal metabolite.

5.3 Preclinical safety data
In animals, extremely high doses (over 100 times the recommended daily dose) have caused oestrogenic effects. There are no other preclinical data of relevance to the prescriber, which are additional to the information included in other sections of the SPC.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate
Povidone K25
Sodium starch glycollate, Type A
Magnesium stearate
Microcrystalline cellulose
Silica, colloidal anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
4 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 packs (PVC film 250 µm, dark green coloured / aluminium foil 20 µm) of 28, 30, 56, 60, 84, 90, 100, 250, 500 and 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Chatfield Pharmaceuticals Limited
Trading as Chatfield Laboratories
Kramer Mews
London SW5 9JL

8 MARKETING AUTHORISATION NUMBER(S)
PL 02142/0050

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/03/2012

10 DATE OF REVISION OF THE TEXT
14/03/2012
UKPAR Tamoxifen 20 mg Tablets

PACKAGE LEAFLET: INFORMATION FOR THE USER

TAMOXIFEN 20 mg TABLETS

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 of the side effects become serious, or if you notice any side effects not listed in
this leaflet, please tell your doctor or pharmacist.

THIS LEAFLET CONTAINS
1. What Tamoxifen is for
2. Before you take Tamoxifen
3. How to take Tamoxifen
4. Possible side effects
5. How to store Tamoxifen
6. Further information

1. WHAT TAMOXIFEN IS FOR

Tamoxifen 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.

This medicine is used to treat:
- breast cancer
- infertility in women caused by a failure to
produce and release eggs (ovulate) properly.

If you are not sure why you have been prescribed these tablets then please ask your
doctor.

2. BEFORE YOU TAKE TAMOXIFEN

Do not take Tamoxifen and tell your doctor if you:
- are allergic (hypersensitive) to Tamoxifen or
any of the other ingredients (listed in section 6
of this leaflet)
- have a family history or genetic predisposition
to blood clots (thromboembolism) and are to
be treated for infertility
- are pregnant, (see section on pregnancy and
breast-feeding below)

Take special care with Tamoxifen

Tell your doctor before you take this medicine if you:
- have a family history of strokes or blood clots
- are going to have or have recently had major
surgery that may cause you to take bed rest or
remain immobile for a long time
- have an inherited blood disorder known as
porphyria
- have not yet gone through the menopause, as
your doctor will have to ensure you are not
pregnant before starting treatment
- are breast-feeding, (see section on pregnancy
and breast-feeding below).

Co-administration with the following drugs should be avoided because a reduction of the effect
of Tamoxifen cannot be excluded; paroxetine, fluoxetine (e.g. antidepressants), buspirone
(anti-depressant or aid to smoking cessation), quinidine (for example used in the treatment
cardiac arrhythmia) and oral contraceptives (for treatment of disorders of the parathyroid glands).

Operations and tests
If you are going to have an operation, (including
planned surgery), tell your doctor you are taking
Tamoxifen. They may suggest that you stop
taking it for a short time.

Taking other medicines
Tell your doctor or pharmacist if you are taking or
have recently taken any other medicines, even
medicines bought without a prescription.

In particular, tell your doctor or pharmacist if you are
taking any of the following medicines, as they
may affect how Tamoxifen Tablets work:
- medicines to treat depression known as
selective serotonin re-uptake inhibitors (SSRIs), such as Duloxetine, Fluoxetine, or
Paroxetine
- medicines to stop blood clots from forming
such as Coumadin, for example Warfarin
- Dronedarone to treat mental health problems
- Rifampicin, an antibiotic used to treat

tuberculosis (TB)
- Etorphine, used to help you stop smoking
- Quindine, used to treat abnormal heartbeats
- Cinacalcet, used to control parathyroid
hormone levels
- other cytotoxic agents, (medicines used in the
treatment of cancer), such as
Cyclophosphamide, Fluorouracil, Methotrexate
or Mitomycin
- hormone preparations used as oral
contraceptives or in hormone replacement
therapy (HRT).

Pregnancy and breast-feeding
Do not take Tamoxifen if you are pregnant, this is
because it may affect your unborn baby.

You should not become pregnant while taking
this medicine or within 2 months of finishing the
course. If you are sexually active, you should use
a barrier method or other non-hormonal method
of contraception. Discuss this with your doctor.

If you think you have become pregnant you
should speak to your doctor immediately.

Do not take Tamoxifen tablets if you are
breast-feeding, unless your doctor has advised
you to take them.

Driving and using machines
Tamoxifen can cause changes in sight and
light-headedness. Do not drive or operate
machinery unless you are sure you are not
affected.

3. HOW TO TAKE TAMOXIFEN

Always take Tamoxifen tablets exactly as
your doctor has told you. You should check
with your doctor/pharmacist if you are not sure.

This medicine is only to be taken by mouth.
Swallow the tablets whole. Tamoxifen tablets
may be taken as a single dose or in divided
doses if appropriate.

Dosage
Your doctor will decide your dose and length of
treatment, as it depends on your condition.

Adults (including the elderly):
Breast Cancer
The usual dose is 20 mg daily.
Infertility
The usual dose is 20 mg daily on days 2, 3, 4,
and 5 of your cycle. Day 1 of the menstrual cycle
is the first day of bleeding. If necessary, the dose
may be increased to 40 mg and then 80 mg for
your next courses. If your cycle is irregular your
course may be started on any day with the next
course starting 45 days later or on day 2 of your
cycle if menstruation occurs. Your doctor will
discuss this with you.
4. POSSIBLE SIDE EFFECTS

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

STOP TAKING Tamoxifen and see a doctor straight away if you:

- have an allergic reaction, which may cause skin rash, itching, red and raised lumps (hives), or swelling of your face or tongue, leading to difficulty in breathing or swallowing
- develop sudden shortness of breath, chest pain, coughing up blood, coughing up blood, coughing up blood, or coughing up blood, or coughing up blood, or swelling in the legs, this could be due to the increased risk of blood clots developing, particularly in the legs (deep vein thrombosis-DVT) or the lungs (pulmonary embolism).

Serious side effects - Tell a doctor straight away if you experience:

- menstrual disturbances, abnormal vaginal bleeding, vaginal discharge, pain or pressure in the pelvis. This could be due to changes in the lining of the womb which may be serious and could include cancer
- inflammation of the lungs. This may show as a dry cough. progressive difficulty in breathing, swelling of the ends of the fingers, bluish discolouration of the skin and fever.
- excessive thirst, nausea or vomiting. You may have too much calcium in your blood and this doctor may want to perform tests.

Other effects:

Very common (affects more than 1 in 10 people)

- hot flashes

Common (affects more than 1 in 100 people)

- nausea
- loss of appetite
- dry mouth
- fatigue
- muscle or bone pain
- feeling sick (nausea)

Uncommon (affects more than 1 in 1,000 people)

- feeling sick (nausea)
- vomiting

Rare (affects more than 1 in 10,000 people)

- temporary disorders of the blood system such as a reduction in blood platelets, which increases risk of bleeding or bruising, or a reduction in the number of white blood cells, which makes infections more likely
- liver problems such as jaundice, which may cause yellowing of the skin or whites of the eyes, or inflammation of the liver (hepatitis)

Very rare (affects less than 1 in 10,000 people, including isolated reports)

- severe blood disorders which can cause weakness, bruising or make infections more likely
- very high cholesterol levels, inflammation of the pancreas which causes fever, nausea and swollen pain in the abdomen and back (pancreatitis)
- liver cell damage
- Stevens-Johnson syndrome, a condition with severe skin rashes, which may also include ring-shaped rashes and the formation of large blisters.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TAMOXIFEN

Keep out of the reach and sight of children.

Store below 25°C and in the original package.

Do not use these tablets after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Tamoxifen tablets contain

The active ingredient in Tamoxifen tablets is Tamoxifen Citrate.

The other ingredients are calcium hydroxide, povidone K29, sodium starch glycolate, magnesium stearate, microcrystalline cellulose and colloidal anhydrous silica.

What Tamoxifen tablets look like and contents of the pack

Tamoxifen 20 mg tablets are round, white tablets with the Chatsfield logo imprinted on one side and with a break-score and “Tamox” imprinted on the other side.

The tablets come in blister packs of 28, 30, 56, 60, 84, 100, 280, 500 and 1000 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Chatsfield Pharmaceuticals Limited, Kemore Mews, London SW5 9JL

Manufacturer

DDSA Pharmaceuticals Limited, 310 Old Brompton Road, London SW5 9QJ

For more information about this product, please contact the Marketing Authorisation Holder.

This leaflet was last revised in 03/2012

Tamoxifen 20 mg Tablets PL 02142/0050
UKPAR Tamoxifen 20 mg Tablets

PL.02142/0050

LABELLING

Tablets for oral use.
Use as directed by the physician.
Please read the enclosed leaflet.
Do not store above 25°C.
Store in the original package.
Store out of the reach and sight of children.

PL.0242/0050 POM

PL holder:
Chatfield Pharmaceuticals Ltd.
Kingsmead, London SW6 5UL

Batch No:
Tamoxifen 20 mg
Tamoxifen 20 mg
Tamoxifen 20 mg
Tamoxifen 20 mg

Expiry Date:

Each tablet contains Tamoxifen Citrate equivalent to 20 mg of Tamoxifen