Public Assessment Report

Tamoxifen 20mg Tablets

Tamoxifen citrate

PL 16363/0135

Milpharm Ltd

Table of Contents

	Page
Lay Summary	2
Scientific Discussion	3
Overall Conclusion And Risk Benefit/Analysis	11
Steps Taken During Assessment	12
Steps Taken After Assessment	13
Summary of Product Characteristics	14
Labels and Leaflet	21

Lay Summary

The MHRA has granted Milpharm Limited a Marketing Authorisation (licence) for the medicinal product Tamoxifen 20mg Tablets (Pl 16363/0135). Tamoxifen is a prescription only medicine that is used in the treatment of breast cancer and in the treatment of anovulatory infertility.

Tamoxifen 20mg Tablets contain the active ingredient tamoxifen citrate. Tamoxifen 20mg Tablets was considered the same as the original product Nolvadex –D 20mg Tablets(AstraZeneca UK Ltd, PL 17901/0034) based on the Quality profile and the bioequivalence study and no new safety concerns arose as a result of this study. It was judged that the benefits of taking Tamoxifen 20mg tablets outweighed the risks, hence a marketing Authorisation was granted.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal product Tamoxifen 20mg Tablets (PL 16363/0135) on 29th August 2007. Tamoxifen 20mg Tablets were shown to correspond to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance and the same dosage form to the reference product (Nolvasex-D 20mg Tablets, PL 17901/0034, Astra-Zeneca Ltd).

Tamoxifen is a prescription only medicine.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Tamoxifen Citrate is 2-[4-[(Z)-1,2-diphenylbut-1-enyl] phenoxy]-N,N-dimethylethanamine dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

$C_{26}H_{29}NO$, $C_6H_8O_7$ MW = 563.6 CAS No: 54965-24-1

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

A current certificate of suitability was provided for the source of the drug substance. The certificate of suitability indicates that:

An appropriate specification has been provided.

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

Tamoxifen is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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.

Appropriate stability data have been generated and support a shelf-life of 5 years.

DRUG PRODUCT

Composition of Drug Product

Tamoxifen
Calcium hydrogen phosphate
Microcrystalline cellulose
Sodium starch glycollate (Type A)
Povidone K25
Magnesium stearate
Colloidal anhydrous silica

All excipients comply with the PhEur and certificates of analysis have been provided. There are no excipients of animal or human origin, the magnesium stearate used is of plant origin. There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

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 batches of the drug product. 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 tablets are in a blister pack of aluminium foil and Polyvinylchloride film which is declared to meet EEC requirements.

Stability

Satisfactory stability data for the finished product has been provided for normal and accelerated conditions and support a shelf-life of 4 years with the instructions store in the original package and do not store above 25°C.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided for this application and none were required.

MEDICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Tamoxifen is a non-steroidal, triphenylethylene-based drug, which displays a complex spectrum of estrogen antagonist and estrogen agonist-like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antiestrogen, preventing estrogen binding to the estrogen receptor.

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4 - 7 hours. Steady state concentrations (about 300 mg/ml) are achieved after four weeks treatment with 40 mg daily. The drug is highly protein bound to serum albumin (> 99%). Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites, which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect. Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the drug itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

PHARMACOKINETICS - BIOEQUIVALENCE STUDY

Study TAM-BIO-EFE-91
This is a study investigating the pharmacokinetics, distribution and the relative bio-availability of tamoxifen in healthy volunteers. The study was an open label, fixed dose study with 5 different study groups.

Study Groups I and II were given either 20mg of Nolvadex or Tamoxifen 20mg Tablets.

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

Results

Tamoxifen 20mg
There were no statistical differences between the treatment groups. Thus the 2 groups can be considered identical based on demographic criteria for age, weight, height and body surface area.

The statistical calculations for the bio-availabilty of tamoxifen and N-desmethyltamoxifen from the reference Nolvadex 20 mg and the applicant tamoxifen 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 20)

Pharmacokinetic	**Nolvadex® 20**					
Parameter	n	mean	SD	CV(%)	Min	Max
C_{max} (ng/ml)	18	31.0	8.8	28.4	18.8	56.9
t_{max}(h)	18	5.28	0.83	15.7	3.00	6.00
AUC_{0-L} (ng·h/ml)	18	2070	540	26.1	1230	3310
$AUC_{0.-oo}$ (ng·h/ml)	18	2250	570	25.3	1320	3510
$t_{1/2}$ (h)	18	126	27	21.4	63.3	180

Pharmacokinetic	**Tamoxifen 20**					
Parameter	n	mean	SD	CV(%)	Min	Max
C_{max} (ng/ml)	18	30.7	6.3	20.5	20.6	43.7
t_{max}(h)	18	5.31	1.30	24.5	2.50	8.00
AUC_{0-L} (ng·h/ml)	18	2030	470	23.2	1040	3120
$AUC_{0.-oo}$ (ng·h/ml)	18	2240	560	25.0	1140	3830
$t_{1/2}$ (h)	18	138	33	23.9	69.7	217

Table 2:
Statistical Results of Testing Treatment with Tamoxifen 20 against Treatment with Nolvadex® 20 Using Mean Square Error Term From 2 Treatment ANOVA

Results for Tamoxifen					
Parameter	**Diff**	**Stat**	**Power**	**90% Sym CI**	**90% Shortest CI**
	(%)			(%)	
C_{max} (ng/ml)	0.8	n.s.d.	0.916	8.40	89.4 to 09.1
t_{max}(h)	0.6	n.s.d.	0.979	6.90	92.4 to 108.8
AUC_{0-L} (ng·h/ml)	2.1	n.s.d.	0.919	9.70	88.1 to 107.7
$AUC_{0.-oo}$ (ng·h/ml)	0.8	n.s.d.	0.906	8.50	89.2 to 109.2
$t_{1/2}$ (h)	9.8	n.s.d.	0.928	17.2	100.2 to 119.4

Results for N-Desmethyltamoxifen					
Parameter	**Diff**	**Stat**	**Power**	**90% Sym CI**	**90% Shortest CI**
	(%)			(%)	
C_{max} (ng/ml)	12.7	n.s.d.	0.433	26.9	69.0 to 105.7
t_{max}(h)	19.5	n.s.d.	0.236	40.0	54.0 to 107.1
AUC_{0-L} (ng·h/ml)	7.7	n.s.d.	0.865	16.0	97.0 to 118.5
$AUC_{0.-oo}$ (ng·h/ml)	6.1	n.s.d.	0.719	16.1	93.2 to 119.1
$t_{1/2}$ (h)	8.5	n.s.d.	0.480	21.8	91.3 to 125.7

Diff: Observed difference between means as % of reference mean

Stat: P value statistic

n.s.d.: no significant difference

90% Sym Cl: 90% confidence interval based on 2 one-sided t-tests (α=0.05) expressed as % of reference mean + 100%

90% Shortest Cl: 90% confidence interval based on 2 one-sided t-tests (α=0.05) expressed as % of reference mean + 100%

N-desmethytamoxifen
The Pharmacokinetic parameters for N desmethyltamoxifen with the 20mg dose of tamoxifen is shown in Table 3, below:

Table 3:
Mean Pharmacokinetic Parameters of N-Desmethyltamoxifen after a Single Oral Dose of 20mg Tamoxifen (Nolvadex® 20 or Tamoxifen 20)

Pharmacokinetic	**Nolvadex® 20**				
Parameter	n	mean	SD	CV(%)	Min	Max
C_{max} (ng/ml)	18	13.3	8.5	63.9	5.82	44.4
t_{max}(h)	18	68.18	50.76	74.4	3.00	192.67
AUC_{0-L} (ng·h/ml)	18	3330	1000	30.0	2040	5620
$AUC_{0.-oo}$ (ng·h/ml)	18	4970	1480	29.8	2770	8110
$t_{1/2}$ (h)	18	295	104	35.3	194	504

Pharmacokinetic	**Tamoxifen 20**				
Parameter	n	mean	SD	CV(%)	Min	Max
C_{max} (ng/ml)	18	11.6	1.8	15.5	9.10	16.2
t_{max}(h)	18	54.90	39.30	71.6	6.00	143.65
AUC_{0-L} (ng·h/ml)	18	3590	780	21.7	2830	5640
$AUC_{0.-oo}$ (ng·h/ml)	18	5270	1730	32.8	3490	9080
$t_{1/2}$ (h)	18	320	147	45.9	166	712

Study Conclusions
Bio-equivalence of 20mg Tamoxifen
The results demonstrate that Nolvadex 20 mg and the applicant's Tamoxifen 20mg Tablet formulation are bio-equivalent for tamoxifen. Bio-equivalence for the metabolite N-desmethytamoxifen is also suggested by the results of this study.

EFFICACY
Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

SAFETY
Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

EXPERT REPORT
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
The applicant has demonstrated bioequivalence for Tamoxifen 20mg Tablets. A Marketing Authorisation may be granted for this product.

Overall Conclusion and Risk/Benefit Analysis

Quality

The 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.

Pre-Clinical

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

Efficay

Bioequivalence has been demonstrated between the applicants Tamoxifen 20mg Tablets and the reference product Nolvadex 20 mg. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Nolvadex 20mg Tablets.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with tamoxifen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 10th July 2002.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 20th September 2002.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 3rd March 2003, February 2004 and on the medical assessment on 7th November 2003, 1st November 2004 and 5th May 2005.
4	The applicant provided further information in regard to the quality assessment on 5th August 2003 and 5th May 2005 and on the medical assessment on 5th August 2003, 1st October 2004, 28th August 2007.
5	The application was determined on 29th August 2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tamoxifen 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg Tamoxifen (as citrate)
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet
White to off-white, round, biconvex, tablets with scoring and '20' embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. The treatment of breast cancer
2. The treatment of anovulatory infertility

4.2 Posology and method of administration

1. Breast cancer

Adults

The recommended daily dose of 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.

Elderly patients
Similar dosing regimens of 'Tamoxifen' have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

2. 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 Tablets must not be given during pregnancy. Pre-menopausal patients must be carefully examined before treatment for breast cancer or infertility to exclude the possibility of pregnancy (see also Section 4.6).

Tamoxifen 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 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 treatment. The underlying mechanism is unknown but may be related to the oestrogen-like effectproperties of Tamoxifen. Any patient receiving or having previously received Tamoxifen 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* patient presents with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. In patients being treated for *infertility*, tamoxifen should not be re-started 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 10mg 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 is 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 is 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 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, although no causal relationship has been established.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

In rodent models of foetal reproductive tract development, tamoxifen was associated with changes similar to those caused by oestradiol, ethynyloestradiol, clomiphene and diethylstilboestrol (DES). Although the clinical relevance of these changes 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 10mg Tablets or within two months of cessation of therapy.

Lactation

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

4.8 Undesirable effects

Side effects can be classified as either due to the pharmacological action of the drug, e.g., hot flushes, vaginal bleeding, vaginal discharge, 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 20 mg/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. An increased incidence of cataracts has been reported in association with the administration of tamoxifen.

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

Cystic ovarian swellings have occasionally been observed in pre-menopausal women receiving tamoxifen.

Leucopenia has been observed following the administration of tamoxifen, 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 is 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 has been associated with changes in liver enzyme levels and on rare occasions with a spectrum of more severe liver abnormalities including fatty liver, cholestasis and hepatitis.

Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen.
An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with Tamoxifen 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 - 20%. 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 mg/ml) are achieved after four weeks treatment with 40 mg daily. The drug is highly protein bound to serum albumin (> 99%). Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites, which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect. Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the drug itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

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 glycollate (Type A)
Povidone K25
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

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

6.5 Nature and contents of container
The tablets are packed in blisters constituted from a PVC and aluminium foil.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Milpharm Limited,
Ares,
Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL16363/0135

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/08/2007

10 DATE OF REVISION OF THE TEXT

29/08/2007

Leaflet and Labels

Milpharm

Patient Information leaflet

KEEP THIS LEAFLET AND READ IT BEFORE YOU TAKE YOUR MEDICINE

Your prescription for Tamoxifen 20mg Tablets

Please read this carefully before you start to use your tablets

- This leaflet contains important information about your treatment. If you have any doubts or questions, or you are not sure about anything, ask your doctor or pharmacist.
- Keep this leaflet. You may need to read this again.
- Your medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

THE LEAFLET CONTAINS INFORMATION ON:

1. What are Tamoxifen Tablets and what are they used for?
2. Information to read before taking Tamoxifen Tablets?
3. How to take your tablets?
4. Can your tablets have any side-effects?
5. Storing your tablets.

The name of your medicine is Tamoxifen Tablets. Each tablet contains active ingredient 20mg tamoxifen (as citrate).
Other ingredients are calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycollate (Type A), povidone K25, magnesium stearate and colloidal anhydrous silica.
Tamoxifen 20mg tablets are available in the blister pack of 30 tablets.

The marketing authorisation holder for Tamoxifen Tablets: Milpharm Limited, Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD, United Kingdom

The tablets are manufactured by: Milpharm Limited, Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD, United Kingdom

1. WHAT ARE TAMOXIFEN TABLETS AND WHAT ARE THEY USED FOR?

What are Tamoxifen Tablets?

Tamoxifen belongs to a group of medicines called anti-estrogens, used in the treatment of breast cancer and anovulatory infertility.
Your doctor may have given you this medicine before from another company and it may have looked slightly different. Either brand will have the same effect.

What are they used for?

Tamoxifen Tablets are used:
- For the treatment of breast cancer
- For the treatment of anovulatory infertility (infertility related to problems with release of eggs in the ovaries)

2. INFORMATION TO READ BEFORE USING TAMOXIFEN TABLETS.

Please take time to read the following information carefully as this may stop you from being able to take Tamoxifen Tablets.

When should you Not take Tamoxifen

Tablets?

Ask yourself the following questions:

- Are you sensitive or allergic to tamoxifen citrate?
- Are you sensitive or allergic to any of the inactive ingredients in Tamoxifen Tablets?
- Are you pregnant or trying to become pregnant?
- Do you have a history or family history of clotting or clotting tendencies
- Are you Breast-feeding

If the answer to any of these questions is YES and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible before taking the tablets.

Warnings/Precautions while taking Tamoxifen Tablets?

Use barrier or non-hormonal contraceptive methods if there are chances of your getting pregnant

Please consult your doctor immediately:

- If you become pregnant while taking tamoxifen.
- If you don't get your periods.
- If you notice abnormal gynaecological symptoms like vaginal bleeding, irregular menstruation, vaginal discharge or pain in pelvic region.
- If you notice development of any tumour in any part of the body

If you have any of these conditions and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking any tablets.
Also consult your doctor if you have any other undesirable effects.

Pregnancy:

Tamoxifen should not be used in pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal abnormalities in women who have become pregnant during tamoxifen treatment. The risk for this occurring persists for 2 months after stopping tamoxifen.. Please use barrier or non-hormonal contraceptive methods if there are chances of your getting pregnant.

Lactation:

Tamoxifen should not be used during lactation as it is found to be excreted in human milk. Please discuss with your doctor if you are breast-feeding before taking your tablets.

Effect on the ability to drive and use machines:

Your tablets are unlikely to have any effect on your ability to drive or use machines.

Taking Tamoxifen Tablets with other medication

It is important to check, whether you are or have recently been taking other medicines before you start taking your tablets. Are you taking any of the following medicines?

- Any anti-coagulant (blood thinning) medicine like warfarin.
- Any anticancer drug.
- Any enzyme inducing medicines such as rifampicin (an anti-tubercular medicine)

Please consult your doctor before starting Tamoxifen Tablets if you are taking any of the above medicines. Also inform your doctor if you are taking or have recently taken, any other medicine including those that you have bought without prescription.

3. HOW TO TAKE YOUR TABLETS?

Breast cancer

Adults:

The recommended daily dose is 20mg daily. Although uncommon, higher doses may also be used. Tamoxifen can be taken in a single daily dose or divided into two doses taken AM and PM.

Elderly patients:

Similar dosing regimen can be used in elderly patients.

If you are going to have a surgery, please tell your doctor that you are on tamoxifen therapy.

Your doctor may want to alter your dose or ask you to stop taking tamoxifen for up to 6 weeks before and during your operation.

Anovulatory Infertility:

In regularly menstruating women, the initial course of treatment consists of 20mg given daily on second, third, fourth and fifth days of menstrual cycle. If required, your doctor may increase the dose to 40mg and then to 80mg in subsequent menstrual cycles.

In women who are not menstruating regularly, the initial course can be given on any day. If your doctor feels necessary, a subsequent course of treatment may start 45 days later with increased dosage.

If you take too many tablets:

It is important to stick to the dose on the label of your medicine. If you or someone else swallows several of these tablets all together, contact your doctor or hospital emergency department immediately. Always take any tablets leftover with you and also the box, as this will allow easier identification of the tablets.

If you forget to take a dose:

If you forget to take a dose, take it as soon as you remember. After that, just carry on as before.

4. CAN YOUR TABLETS HAVE ANY SIDE-EFFECTS?

Like many medicines, Tamoxifen Tablets may cause side effects in some patients. The majority of side effects seen with tamoxifen have been mild and do not cause patients to stop taking their medicine.

The most common side effects reported with tamoxifen are hot flushes, vaginal discharge or bleeding and menstrual irregularities, stomach upset, fluid retention. Women may experience hair loss, skin rashes (itching or peeling skin) or headaches or inflammation of the lungs, which may have the same symptoms as pneumonia, such as breathlessness and cough.

A rare but serious side effect of tamoxifen is blood clot in the veins. Blood clots stop the flow of blood and can cause serious medical problems, disability or death. Women who take tamoxifen are at increased risk for developing blood clots in the lungs and legs. Some women may develop more than one blood clot, even if tamoxifen is stopped. Women may also have complications from treating a clot, such as bleeding from thinning the blood too much. Symptoms of blood clot in the lungs may include sudden chest pain, shortness of breath or coughing up blood. Symptoms of blood clot in the legs are pain or swelling in the calves. A blood clot in the legs may move into the lungs. If you experience any of these symptoms of blood clot, contact your doctor immediately.

Tamoxifen increases the chance of having a stroke, which can cause serious medical problems, disability or death. If you experience any symptoms of stroke such as weakness, difficulty in walking or talking, or numbness, contact your doctor immediately.

Tamoxifen increases the chance of changing in the lining (endometrium) or body of your uterus,

which can be serious and include cancer. If you had not had a hysterectomy (removal of uterus), contact your doctor immediately if you experience any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities; or pain or pressure in pelvis (lower stomach).These may be caused by changes to the lining or body of your uterus. Please contact your doctor immediately if you notice any such problem.

Tamoxifen may also lead to the development of ovarian cysts.

Tamoxifen can cause cataract or changes to parts of eye known as the cornea or retina. Tamoxifen can increase the chance of needing contract surgery and can cause blood dots in the veins of the eye. Tamoxifen can result in difficulty in distinguishing different colours. If you experience any changes in your vision, tell your doctor immediately.

Rare side effects, which may be serious, include certain liver problems such as jaundice (which may be seen as yellowing of the whites of the eye) or hypertriglyceridemia (increased levels of fat in the blood) sometimes with pancreatitis (pain or tenderness in the upper abdomen), difficulty in swallowing, swelling of hands, feet, ankles, nettle rash and 'hives'. Stop taking tamoxifen and contact your doctor immediately if you develop angioedema (swelling of the face, lips, tongue and/or throat) even if you have been taking tamoxifen for a long time.

If you are a women receiving tamoxifen for treatment of advanced breast cancer, and you experience excessive nausea, vomiting or thirst, tell your doctor immediately. This may mean that there are changes in the amount of calcium in your blood (hypercalcemia). Your doctor will evaluate this.

In patients with breast cancer, a temporary increase in the size of the tumor may occur and sometimes results in muscle aches/bone pain and skin redness. This condition may occur shortly after starting tamoxifen and may be associated with a good response to treatment.

Tamoxifen can cause tendency to bruise or bleed more easily.

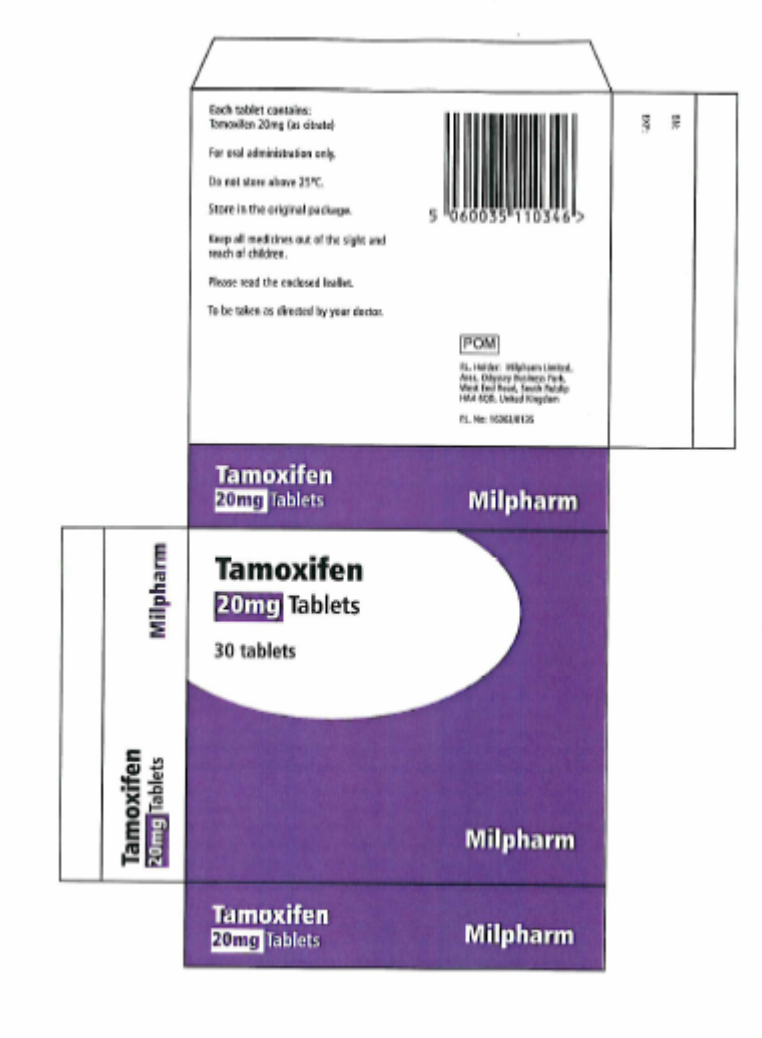
Many of these side effects happen only rarely. However, you should contact your doctor if you think that you have any of these or any other problems with your tablets. Some side effects of tamoxifen may become apparent soon after starting the drug, but others may appear at any time during therapy.

5. STORING YOUR TABLETS.

- Store your tablets in the original package.
- Do not store above 25ºC
- On the label you will find a date after which the medicine is no longer fit for use. Do not use this medicine after this date
- If you have any tablets, which are out of date, return them to your pharmacist for disposal.
- Store away from heat and direct sunlight
- Do not store in bathroom, near the kitchen sink, or in damp places. Heat or moisture may cause the medicine to break down
- Keep out of the reach and sight of children

Remember : This treatment is only for YOU . Only a doctor can prescribe it to others. Never give it to others.

Date of preparation : August 2007


Each tablet contains:
Tamoxifen 20mg (as citrate)
For oral administration only.
Do not store above 25°C.
Store in the original package.
Keep all medicines out of the sight and reach of children.
Please read the enclosed leaflet.
To be taken as directed by your doctor.
5 060035 110346
POM
Tamoxifen
20mg Tablets
Milpharm
Tamoxifen
20mg Tablets
30 tablets
Milpharm
Tamoxifen
20mg Tablets
Milpharm
Tamoxifen
20mg Tablets
Milpharm