Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UK PAR

Tamoxifen 20mg Tablets

(tamoxifen citrate)

UK Licence No: PL 16363/0135

Milpharm Limited

LAY SUMMARY

Tamoxifen 20mg Tablets

(tamoxifen citrate)

This is a summary of the Public Assessment Report (PAR) for Tamoxifen 20 mg Tablets (PL 16363/0135). For ease of reading, Tamoxifen 20mg 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.

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' medicine'. This means that Tamoxifen is similar to a 'reference medicine' called Nolvadex-D 20 mg tablets (PL 17901/0034; AstraZeneca UK Limited, UK), which was 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 healthcare 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 they are 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 the 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 a tablet. The tablets should be swallowed with a glass of water.

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 their 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.

Use in children and adolescents

Children and adolescents should not take Tamoxifen.

What benefits of Tamoxifen has been shown in studies?

As Tamoxifen is a 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 Milpharm Limited on 29 August 2007.

A variation to add the indication ‘primary prevention of breast cancer in women at moderate or high risk’ was granted on 19 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 UK granted a Marketing Authorisation for the medicinal product Tamoxifen 20mg Tablets (PL 16363/0135) on 29 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 (Nolvadex-D 20mg Tablets, PL 17901/0034, Astra-Zeneca Ltd).

Tamoxifen is a prescription only medicine.

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

Each tablet contains 20 mg of tamoxifen (as citrate). Other ingredients consist of the pharmaceutical excipients calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycollate (Type A), Povidone K25, magnesium stearate and colloidal anhydrous silica. Appropriate justification for the inclusion of each excipient has been provided.

II.2 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.

II.3 Medicinal 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 their respective European Pharmacopoeia monographs and satisfactory 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 special storage instructions ‘Do not store above 25°C. Store in the original package.’

Conclusion
The grant of a Marketing Authorisation is recommended, from a quality point view.

III NON-CLINICAL ASPECTS

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

The grant of a Marketing Authorisation is recommended, from a non-clinical point view.

IV. CLINICAL ASPECTS

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-availability 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 Cl**	**90% Shortest Cl**	
	(%)			(%)		
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 Cl**	**90% Shortest Cl**	
	(%)			(%)		
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 (SmPC)
This is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory.

CONCLUSION
The applicant has demonstrated bioequivalence for Tamoxifen 20mg Tablets. A Marketing Authorisation may be granted for this product, from a clinical point of view.

V. USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
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VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

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.

Non-Clinical
No new non-clinical data were submitted and none are required for this type of application.

Efficacy
Bioequivalence has been demonstrated between the applicant's Tamoxifen 20mg Tablets and the reference product Nolvadex 20 mg. No new or unexpected safety concerns arose from this application.

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

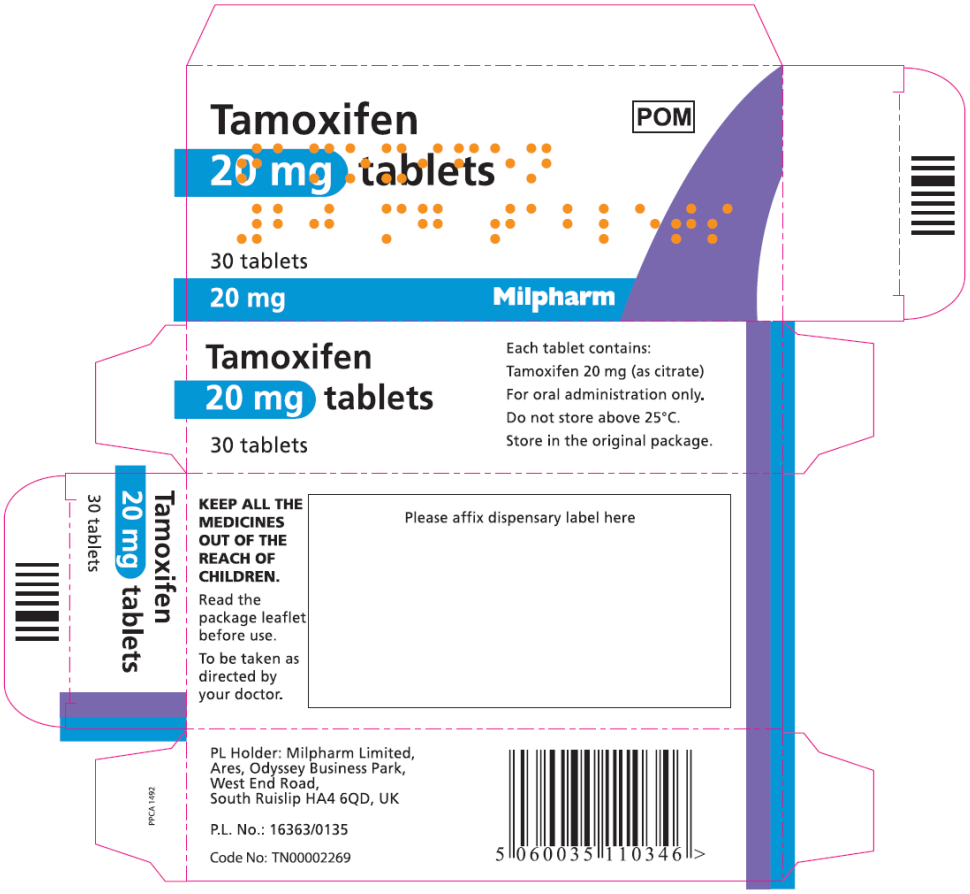
Risk/Benefit Analysis

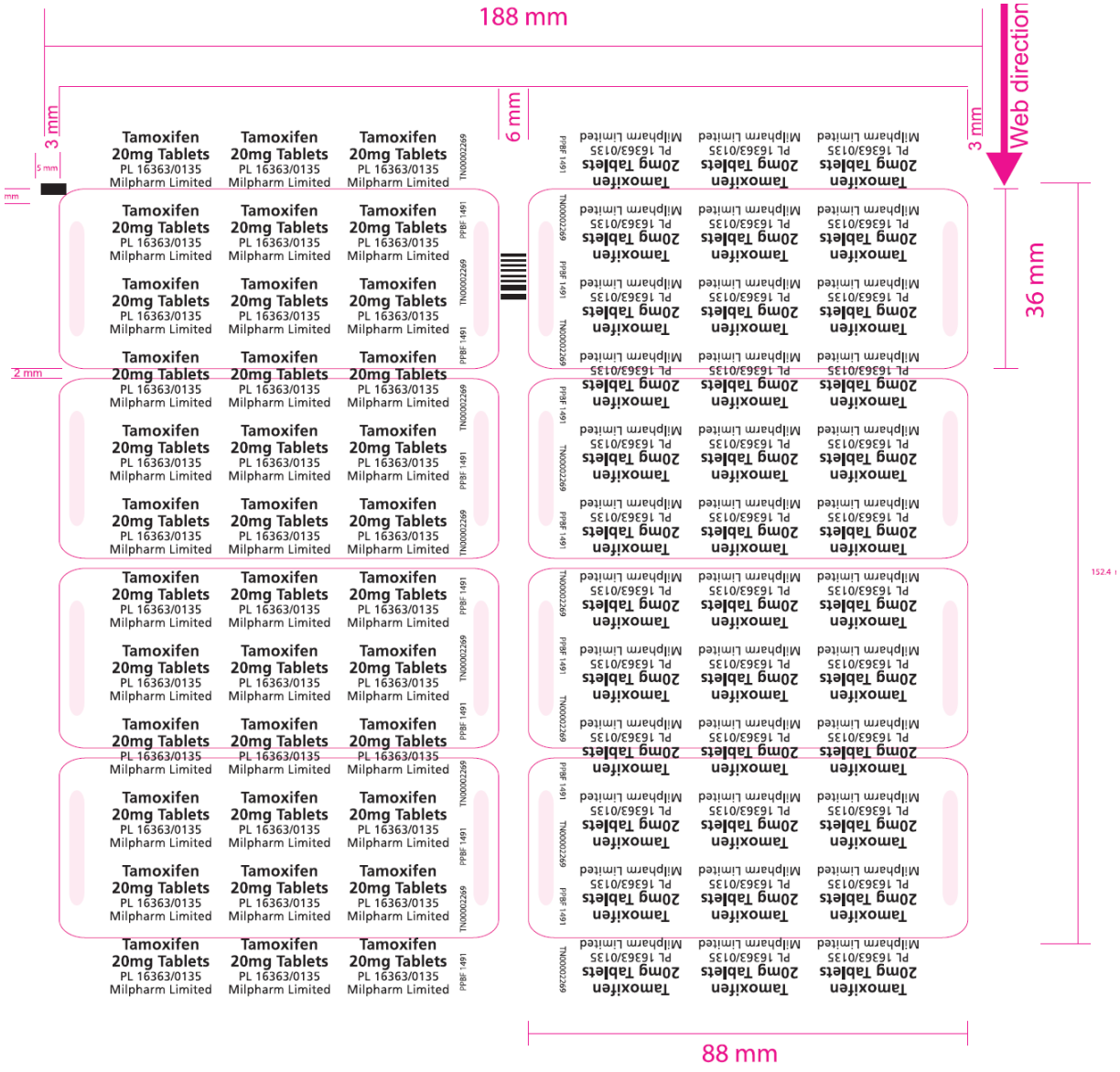
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with tamoxifen is considered to have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

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.

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:




188 mm
Web direction
3 mm
6 mm
3 mm
36 mm
2 mm
88 mm
Tamoxifen
20mg Tablets
PL 16363/0135
Milpharm Limited

Tamoxifen 20 mg Tablets

(tamoxifen citrate)

PL 16363/0135

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

The following table lists a non-safety update to the Marketing Authorisation for Tamoxifen 20mg Tablets (PL 16363/0135) that have been approved by the MHRA since the Marketing Authorisation was approved. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
15/06/2018	Type IB	1. To update sections 4.1, 4.2, 4.3, 4.4. 4.5, 4.8 and 5.1 of the SmPC in line with the reference product for Tamoxifen 20mg Tablets. Consequently, impacting the PIL. 2. To introduce a new Risk Management Plan (RMP)	Approved on 19 July 2018

Annex 1

Our Reference: PL 16363/0135, Application 0022
Product: Tamoxifen 20mg Tablets
Marketing Authorisation Holder: Milpharm Limited
Active Ingredient(s): Tamoxifen citrate

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
1. To update sections 4.1, 4.2, 4.3, 4.4. 4.5, 4.8 and 5.1 of the SmPC in line with the reference product for Tamoxifen 20mg Tablets. Consequently, impacting the PIL.
2. To introduce a new Risk Management Plan (RMP).

Supporting Evidence
Revised SmPC fragments
Updated PIL
New 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 19 July 2018