CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Letrozol Synthon 2.5 mg, film-coated tablets
Synthon B.V., the Netherlands

Letrozole

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1179/01/DC
Registration number in the Netherlands: RVG 100787

9 April 2009

Pharmacotherapeutic group:	Enzyme inhibitors
ATC code:	L02BG04
Route of administration:	oral
Therapeutic indications:	hormone-dependent breast cancer in postmenopausal women
Prescription status:	prescription only
Date of authorisation in NL:	9 January 2009
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Letrozol Synthon 2.5 mg, film-coated tablets, from Synthon B.V.. The date of authorisation was on 9 January 2009 in the Netherlands.

The product is indicated for:
- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of hormone-dependent early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer in women with natural or artificially induced postmenopausal status after relapse or disease progression, who have previously been treated with anti-oestrogens.

Efficacy has not been demonstrated in patients with hormone-receptor negative breast cancer.

A comprehensive description of the indications and posology is given in the SPC.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Femara 2.5 mg film-coated tablets (NL License RVG 20755) which has been registered in France by Novartis Pharma since 1996 and via a MRP (FR/H/0110/01) in several CMSs including the NL. In addition, reference is made to Femara authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This legal basis of these applications is considered acceptable for the following reason:
- The applications refer to a reference product which has been authorised under article 6 of Dir 2001/83/EC as amended for not less than 6/10 years in the EEA.
- The products have the same qualitative and quantitative composition in active substance as the reference product.
- The products have the same pharmaceutical form as the reference product.
- Bio-equivalence to the reference product has been demonstrated by appropriate bioavailability studies.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Femara tablets, registered in Spain. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General information
The active substance is letrozole, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is practically insoluble in water. The molecule is optically inactive and does not exhibit polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of a two step synthesis followed by a purification step. No Class 1 organic solvents are used. The manufacturing process does not require heavy metal catalysts. The active substance was adequately characterized. Acceptable specifications were adopted for the starting materials, solvents, and reagents.

Quality control of drug substance
The drug substance specification is in line with the European Pharmacopoeia, with additional requirements for residual solvents, heavy metals, and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches.

Stability of drug substance
Stability data on the active substance were provided for three commercial scale batches stored at 25°C/60% RH (eighteen months) and 40°C/75% RH (six months). The drug substance remained stable under accelerated and long term storage conditions for all parameters tested. On the basis of the available stability data, a re-test period of 30 months has been granted. The drug substance does not require specific storage conditions. The MAH committed to continue the stability studies on the drug substance up to 36 months and to provide the data when available.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Letrozol Synthon 2.5 mg film-coated tablets contain as active substance 2.5 mg of letrozole, and are yellow, round, biconvex, film-coated tablets, debossed with “L9OO” on one side and “2.5” on the other side.

The film-coated tablets are packed in carton boxes containing PVC/Aluminium blisters with 10, 28, 30, 50, 60, 84, 90, 98 or 100 tablets per box.

The excipients of the core are lactose monohydrate, microcrystalline cellulose, pregelatinised maize starch, sodium starch glycolate, magnesium stearate, and colloidal silicon dioxide. The coating material is composed of hypromellose, macrogol, talc, titanium dioxide, and iron oxide yellow. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The objective was to develop a product that would be essentially similar to the innovator product Femara 2.5 mg film-coated tablets. The development of the product has been described, the choice of the excipients is justified and their functions explained. Pharmaceutical development focused on optimizing the mixing process in order to obtain a blend which is suited for direct compression. Particle size turned out to be critical for dissolution. An appropriate limit was included in the specification of the drug substance. A bioequivalence study was performed by comparing a commercial scale batch produced during process validation with a Spanish reference product. The products can be regarded as similar without further mathematical evaluation. The packaging material is commonly used for solid oral dosage forms. Moreover, the suitability of the packaging material was tested in stability studies. The pharmaceutical development of the product was adequately performed.

Manufacturing process and quality control of the medicinal product
The manufacturing process uses conventional manufacturing techniques. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented in accordance with the relevant European guidelines for 3 commercial scale batches produced by one production site and for 3 commercial scale batches produced by a second production site. The size of these batches was at the lower proposed batch size range. The MAH therefore committed to validate the first three maximum sized batches post authorisation.

Quality control of drug product
The product specification includes tests for appearance, disintegration, identification, assay, uniformity of dosage units, impurities, microbial contamination, and identification of colorants. The MAH committed to test for microbial contamination on at least three consecutive industrial batches of the drug product.

The limits for total impurities at release and at the end of shelf life are not supported by the available batch analysis results and stability data. Therefore, the applicant should re-evaluate the limits for total impurities at release and at the end of shelf life when more stability data is available. The MAH committed to demonstrate accuracy between the disregard limit and the specification limit of the drug product.

The analytical methods were adequately described. Validation data was provided for the HPLC methods for identification, the assay, and related substances and for the TLC method for identification.
Batch analytical data from 3 commercial scale batches from the proposed production sites have been provided, demonstrating compliance with the release specification.

Excipients
All excipients including the components of the coating material comply with the European Pharmacopoeia. For the coating material, a separate specification was provided. The specifications are acceptable.

Stability tests on the finished product

Stability data on the product have been provided for 3 commercial scale batches stored at 25°C/60%RH (twelve months) and at 40°C/75% RH (six months). In addition, photostability was tested. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed commercial packaging.
Except for a small decrease in dissolution time, no specific trends were observed for any of the tested parameters at accelerated and long term storage conditions. Photostability was demonstrated.
The proposed shelf-life of 24 months is justified. The drug product does not require special storage conditions. Additional stability data needed to fully support the claimed shelf-life should be provided when available. The MAH committed to continue the long term stability studies on active substance and finished product according to the established protocols, and to report any deviation to the member states concerned.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin. A Statement confirming compliance of lactose monohydrate with the criteria of the Note for Guidance on TSE/BSE (milk sourced from healthy animals under the same conditions as milk collected for human consumption) was provided.

II.2 Non clinical aspects

This product is a generic formulation of Femara 2.5 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of letrozole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Letrozole is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Letrozol Synthon 2.5 mg tablets is compared with the pharmacokinetic profile of the Spanish reference product Femara 2.5 mg tablets.

A single-dose, randomised, crossover, comparative bioequivalence study was carried out under fasted conditions in 24 (+ 4 alternates) healthy male subjects, age between 18 and 38 years with BMI between 18.6-29.6 kg/m^2. Each subject received a single dose (2.5 mg) of one of the 2 letrozole formulations. One film-coated tablet was administered with 240 ml water, after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of at least 3 weeks. Venous blood samples (3 ml each) were collected at pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168, 216, and 288 hours after administration of the products.
Three subjects dropped out after the first treatment because of flu-like symptoms and tiredness and were replaced by three alternates before analysis. Twenty-five volunteers completed the study, and 24 volunteers were used for pharmacokinetic analysis as described in the protocol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of letrozole under fasted conditions.

Treatment N= 24	**AUC_{0-t}** ng./ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1483 ± 574	1613 ± 611	30.7 ± 5.9	1.5 (0.67-3.0)	48 ± 17

Reference	1511 ± 566	1629 ± 628	30.2 ± 4.9	1.5 (0.67-4.0)	48 ± 17
***Ratio (90% CI)**	0.98 (0.93-1.03)	0.99 (0.95-1.03)	1.01 (0.97-1.06)	-	-
CV (%)	10.1%	7.7%	9.6%	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Letrozole can be taken without reference to food intake; therefore, demonstration of bioequivalence under fasting conditions is in agreement with the CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence. No unexpected adverse events related to drug treatment were observed.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of letrozole under fasted conditions, it can be concluded that Letrozol Synthon 2.5 mg tablets and reference Femara® 2.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Letrozole was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of letrozole can be considered to be well established and no product specific pharmacovigilance issues were identified pre or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product.

Pharmacovigilance system
The member states consider that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH 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.

Product information

SPC
The SPC has been adapted to the texts of the reference product Femara (FR/H/110/II/43) marketed by Novartis Pharma and according to the comments from the member states.

Package leaflet
The package leaflet has been amended to be in line with the last approved package leaflet for Femara. Comments from the member states have been implemented in the text.

Readability test
The package leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1). Three rounds of testing including a pilot test were performed with

a total of 22 participants. The participants were potential users, women >45 years. One potential carer, male >45 was included in the 2nd round of testing.

The questionnaire consisted of 15 questions. Three additional questions requesting feedback of the participant on the layout, design and friendliness of the PIL were also included.
The result scores were very high. In the 1st round, for all questions 100% of participants were able to find the correct information and to answer each question correctly.
In the 2nd round, for 14 questions 100% of participants were able to find the correct information and answer correctly, for the remaining question 90% of the participants were able to find the correct information and answer correctly. As result of the high scores, no modifications were made to the PIL after the 1st or 2nd round of testing.

The results of the test indicate that the PIL for Letrozol Synthon 2.5 mg film-coated tablets, fulfils the requirements of readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Letrozol Synthon 2.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Femara 2.5 mg film-coated tablets. Femara 2.5 mg is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC has been adapted to the texts of the reference product Femara (FR/H/110/II/43) marketed by Novartis Pharma and according to the comments from the member states. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other letrozole containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Letrozol Synthon 2.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 October 2008. Letrozol Synthon 2.5 mg was authorised in the Netherlands on 9 January 2009.

A European harmonised birth date has been allocated (24 July 1996) and subsequently the first data lock point for Letrozole is 31 October 2008. The first PSUR should be submitted using the data lock point of October 2011 (submission December 2011). Because the procedures were finalised on 13 October 2008, the period covering 14 to 31 October 2008 should be submitted as addendum with the first PSUR. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be: October 2013

The following post-approval commitments have been made during the procedure:

<u>Quality - active substance</u>

- The MAH committed to continue the stability studies on the drug substance up to 36 months and to provide the data when available.

<u>Quality - medicinal product</u>

- The MAH committed to validate the first three maximum sized production batches.
- The MAH committed to demonstrate accuracy between the disregard limit and the specification limit.
- The MAH committed to test for microbial contamination on at least three consecutive industrial batches of the drug product.
- The MAH committed to continue the long term stability studies on active substance and finished product according to the established protocols, and to report any deviation to the member states concerned.
- The MAH committed to re-evaluate the limits for total impurities at release and at the end of shelf life when more stability data is available.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached