CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Letroman 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/1687/001/DC
Registration number in the Netherlands: RVG 104889

5 January 2011

Pharmacotherapeutic group:	Enzyme inhibitors
ATC code:	L02BG04
Route of administration:	oral
Therapeutic indication:	hormone-dependent breast cancer in postmenopausal women
Prescription status:	prescription only
Date of authorisation in NL:	20 December 2010
Concerned Member States:	Decentralised procedure with DE, FR, UK
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 Letroman 2.5 mg, film-coated tablets from Synthon B.V. The date of authorisation was on 20 December 2010 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. The main source of oestrogen is through changing androgens (sex hormones produced by the adrenal glands) into oestrogen. This is carried out by an enzyme called aromatase. The conversion process is known as aromatisation, and happens mainly in the fatty tissue of the body. Letrozole blocks (reversibly) this process, resulting in a reduction of oestrogen biosynthesis in all tissues where present. Many breast cancers rely on supplies of the hormone oestrogen to grow.

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. 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 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 2.5 mg 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, and no paediatric development programme has been submitted, as this is not required for a generic medicinal product.

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
The active substance is letrozole, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or yellowish, crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in methanol. 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/EMA 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 the drug substance specification were provided for three commercial-scale batches.

Stability of drug substance
Stability data on the active substance were provided for three commercial scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The batches were adequately stored. The drug substance remained stable under accelerated and long term storage conditions for all parameters tested. No specific trend was observed. On the basis of the available stability data, the claimed re-test period of 36 months is justified. The drug substance does not require specific temperature storage conditions.

* *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
Letroman 2.5 mg is a yellow, round, biconvex film-coated tablet, debossed with 'L9OO' on one side and '2.5' on the other side.

The film-coated tablets are packed in PVC/aluminium blisters.

The excipients are:

Tablet core - lactose monohydrate, microcrystalline cellulose (E460), pregelatinised maize starch, sodium starch glycolate type A, magnesium stearate (E572), colloidal anhydrous silica (E551).
Coating - macrogol 8000, talc (E553b), hypromellose (E464), titanium dioxide (E171), iron oxide yellow (E172).

Pharmaceutical development
The development of the product has been described, the choice of 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. *In vitro*, more than 85% of both the test and the reference product were dissolved within 15 minutes. The products can therefore 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
The manufacturing process consists of a three step blending process followed by direct compression and coating, which are regarded as conventional manufacturing techniques. The manufacturing process was adequately validated according to relevant European guidelines. Process validation data on the product was presented for six commercial-scale batches produced by one production site and for three commercial-scale batches produced by a second production site. The MAH committed to validate the first three maximum sized batches produced at each site post authorisation.

Control of excipients
With the exception of the coating material, all excipients comply with the European Pharmacopoeia. For the coating material, a separate specification was provided. The specifications are acceptable.

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 colourants. Except for widened shelf life limits for the largest unidentified impurity, total unidentified impurities, and total impurities, the release and shelf-life limits are identical. The analytical methods were adequately described. Batch analytical data from each of the proposed production sites were provided on three-commercial scale batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product was provided on three commercial-scale batches stored at 25°C/60%RH (36 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 and one batch in bulk 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 3 years could therefore be granted. The drug product does not require special storage conditions.
MAH committed to re-evaluate the release and shelf-life limits of total impurities when stability data covering the whole shelf-life are available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only ingredient of animal origin. A statement declaring compliance with the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy* (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 a bioequivalence study in which the pharmacokinetic profile of the test product Letroman 2.5 mg film-coated tablets (Synthon B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Femara 2.5 mg tablets (Novartis, Spain).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, crossover bioequivalence study was carried out under fasted conditions in 28 (24 + 4 alternates) healthy male subjects, aged 18-38 years. Each subject received a single dose (2.5 mg) of one of the 2 letrozole formulations. The tablet was orally 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.

Blood samples were collected 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.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Three subjects dropped out after the first because of flu like symptoms and tiredness and were replaced by alternates before analysis. Twenty-five subjects completed the study. Twenty-four subjects were included in the pharmacokinetic analysis as per 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.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**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*

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 Letroman 2.5 mg and 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.

Letrozole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of letrozole. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The SPC has been brought in line with the last approved SPC for the innovator Femara, FR/H/110/II/047.

Readability test

The 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The participants were potential users, women >45 years. One potential carer, male >45, was included in the second 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

In the first round, for all questions 100% of participants were able to find the correct information and to answer each question correctly. In the second round, for 14 questions 100% of participants were able to find the correct information, for the remaining one 90% of the participants were able to find the correct

information. Similarly, for 14 questions 100% of participants were able to answer each question correctly, for the remaining one 90% of the participants were able to answer each question correctly.
As result of the high scores, no modifications were made to the PIL after the test rounds. No suggestions for improvement were made as a result of the participants' opinions on the leaflet.
The readability test has been sufficiently performed. The results of the test indicate that the PIL fulfils the requirements of readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Letroman 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 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, 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 Letroman 2.5 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 9 April 2010. Letroman 2.5 mg, film-coated tablets was authorised in the Netherlands on 20 December 2010.

A European harmonised birth date has been allocated (24 July 1996) and subsequently the first data lock point for letrozole is October 2011. The first PSUR will cover the period from April 2010 to October 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 9 April 2015.

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

Quality - medicinal product

- The MAH committed to re-evaluate the release and shelf-life limits of total impurities when stability data covering the whole shelf-life are available.
- The MAH committed to validate the first three batches per manufacturing site when the batch size will be further increased to the maximum batch size.

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
Change in the name of the medicinal product in DE.	NL/H/1687/ 001/IB/002	IB	15-10-2010	15-11-2010	Approval	N