CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Letrozol Glenmark 2.5 mg film-coated tablets
Glenmark Pharmaceuticals (Europe) Ltd., United Kingdom

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/1452/001/DC
Registration number in the Netherlands: RVG 102781

18 January 2010

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:	28 October 2009
Concerned Member States:	Decentralised recognition procedure with BG, CZ, EE, HU, LT, LV, PL, PT, RO, 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 Glenmark 2.5 mg film-coated tablets, from Glenmark Pharmaceuticals (Europe) Ltd. The date of authorisation was on 28 October 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. 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 including 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 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 2.5 mg, registered in Ireland. 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 application.

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 drug substance is a white or yellowish, crystalline powder which is practically insoluble in water, freely soluble in methylene chloride, and sparingly soluble in methanol. Letrozole is optically inactive and does not show 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
Letrozole is prepared from the in-house starting material via a one-step synthesis and subsequent purification. No Class 1 solvents are used. Synthesis does not involve 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 Ph.Eur., with additional requirements for residual solvents and particle size. The specification is acceptable in view of the route of synthesis and the various ICH 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 drug substance remained stable at both storage conditions. Based on the data provided, the claimed re-test period of 36 months could be granted. No special storage conditions are required.

** 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 Glenmark 2.5 mg contains is a yellow, round, biconvex, film-coated tablet, debossed "2.5" on one side, plain on reverse.

The film-coated tablets are packed in blister of PVC/PVdC and hard tempered aluminium foil.

The excipients are:
Tablet core – microcrystalline cellulose, anhydrous colloidal silica, sodium starch glycollate (Type A), magnesium stearate.

Tablet coating - Opadry II Yellow 85F38026 consisting of: polyvinyl alcohol, polyethylene glycol, titanium dioxide (E171), talc, yellow iron oxide (E172), sunset yellow FCF (E110).

Pharmaceutical development
The development of the product was described, the choice of excipients justified and their functions explained. The excipients used are common in the manufacture of film-coated tablets and allowed a direct compression approach. It was shown that the drug substance needed to be micronised to achieve a dissolution profile which was similar to the reference product. The choice of the manufacturing process is justified. The packaging is usual and suitable for the product at issue.
A batch of the smallest proposed commercial batch size was used for the bioequivalence studies. It was compared to the Irish reference product. More than 85% of the generic and the reference product were dissolved after 15 minutes indicating that the dissolution profiles are similar.
The pharmaceutical development of the product was adequately performed.

Manufacturing process
The product is manufactured using conventional manufacturing techniques involving direct compression of the final blend followed by film-coating. The manufacturing process was adequately validated according to relevant European guidelines. Process validation data was presented for two commercial scale batches of tablets among which the batch used in the bioequivalence study. Process validation for the larger proposed batch sizes will be performed post authorization.

Excipients
With the exception of silicified microcrystalline cellulose and the coating material, the excipients comply with the Ph.Eur. Acceptable in-house specifications were developed for silicified microcrystalline cellulose (Prosolv) and the coating material.

Quality control of drug product
The product specification for the tablets includes tests for appearance, average weight, identification of the drug substance and of colourants, dissolution, related substances, assay, content uniformity, and microbial limits. The release and end of shelf life requirements are identical and considered to be acceptable.
The analytical methods were adequately described and validated. Batch analysis data were provided for four batches produced at both manufacturing sites. The data demonstrated compliance with the release specification.

Stability of drug product
Stability data on the product was provided for four batches (two per manufacturing site) stored at 25°C/60% RH (18 and six months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline.The drug product was packed in the commercial packaging, i.e., Al/PVC-PVdC blisters, and stored in bulk. Except for a slight decrease in dissolution and a slight increase in related substances, no trends or significant changes were observed in any of the tested parameters under both accelerated and long term storage conditions. The drug product was shown to be photostable. Based on the available stability data, a shelf-life of two years could be granted. No special storage conditions are required.
The MAH committed to place the first three batches of the larger proposed batch sizes on stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE declarations were provided for the active substance, excipients and the packaging materials.
None of the components is made from or comes in contact with products of human or animal origin.

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 Glenmark 2.5 mg (Glenmark Pharmaceuticals ltd, UK) is compared with the pharmacokinetic profile of the reference product Femara 2.5 mg tablets (Novartis, Ireland).

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, two-treatment crossover bioequivalence study was carried out under fasted conditions in 18 healthy male subjects, aged 19-45 years. Each subject received a single dose (2.5 mg) of one of the 2 letrozole formulations. 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, 1.0, 1.5, 2, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 24, 48, 72, 120, 168, 216 and 288 hours after administration of the products.

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.

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
All 18 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=18	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1526 ± 452	1574 ± 458	33 ± 6	1.50 (0.66-3.00)	45 ± 8
Reference	1474 ± 451	1538 ± 424	34 ± 7	1.50 (0.66-6.00)	45 ± 8
***Ratio (90% CI)**	1.04 (0.98-1.10)	1.02 (0.98-1.06)	0.98 (0.91-1.06)		

CV (%)	10	7	13		

$AUC_{0-\infty}$ 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 Letrozol Glenmark 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.

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 postauthorisation 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 adapted to the most recently SPC for the innovator Femara, approved after variation II-44 (FR/H/110/01/II/44), and according to the comments from the member states.

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 questionnaire consisted of 15 questions. Three additional questions requesting feedback of the participants on the lay-out, 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, 98% of participants were able to find the correct information, and 98% of participants were able to answer the questions correctly. No modifications were made to the PIL after the first or second round of testing.

The responses to the three additional questions concerning the layout, design and friendliness of the PIL were only recorded as a matter of reference. The PIL is well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable and patients/users are able to act upon the information that it contains. The requirements of readability have been fulfilled.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Letrozol Glenmark 2.5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Femara 2.5 mg 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Letrozol Glenmark 2.5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 July 2009. Letrozol Glenmark 2.5 mg film-coated tablets was authorised in the Netherlands on 28 October 2009.

A European harmonised birth date has been allocated (24 July 1996) and subsequently the first data lock point for Letrozole is 31 October 2011. The first PSUR will cover the period from July 2009 to October 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 2 July 2014.

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

Quality - medicinal product

- The MAH committed to carry out process validation on one additional pilot-scale batch and the first three production batches of the proposed batch sized from both manufacturers.
- The MAH committed to continue the ongoing stability studies of the batches up to the claimed shelf life of two years, and to place the first three post-approval batches on stability.
- The MAH committed to provide the results of the ongoing stability studies up to the claimed shelf life.

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