CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Letrozol Sandoz 2.5 mg film-coated tablets Sandoz 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/1814/001/DC
Registration number in the Netherlands: RVG 106323

24 November 2010

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:	2 November 2010
Concerned Member States:	Decentralised procedure with DE
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 Sandoz 2.5 mg, film-coated tablets from Sandoz B.V. The date of authorisation was on 2 November 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. The widely accepted means of demonstrating this is a bioequivalence study. However, the current application does not include a comparative bioavailability or bioequivalence study. Reference is made to fulfilling all requirements for a biowaiver. See paragraph II.3 "Clinical Aspects".
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 to yellowish crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in methanol. The substance is not chiral and 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
Letrozole is synthesized in a three step process. No class 1 solvents or heavy metal catalysts are used. The substance has been adequately characterized, and acceptable specifications have been adopted for the starting material, 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, heavy metal, sulphated ash, particle size, absorbance and clarity of solution. 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 have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 5 pilot-scale batches and 1 lab-scale batch stored at 25°C (60 months), and 40°C (24 months). No changes were seen in the stability studies. The re-test period of 60 months is justified. No specific storage condition is considered necessary, but the condition 'store below 30 °C' is acceptable. Additional stability data of storage at the additional production site covering 3 months storage, is consistent with the known stability results.

* *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 Sandoz 2.5 mg is a dark yellow, slightly biconvex tablet with bevelled edges. One side bears the imprint "FV", the other "CG".

The film-coated tablets are packed in PVC/PE/PVDC/aluminium blister packs.

The excipients are:

Tablet core - lactose monohydrate, cellulose microcrystalline (E460), maize starch, sodium starch glycolate, magnesium stearate (E572), silica colloidal anhydrous (E551).
Coating - hypromellose (E464), talc (E553b), macrogol 8000, 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. The optimization process of the formulation and manufacture has been sufficiently described. Dissolution profiles using media with different pH values were compared. No influence of the different pH-values from the range of pH 1.0 to 6.8 on the dissolution profiles was observed. The dissolution profiles of test and innovator products were compared. Both test and innovator products dissolve rapidly.
The *in vitro* dissolution is more rapid than the calculated *in vivo* dissolution. Since the dosage scheme provides for only one tablet per day, the speed of dissolution is regarded as insignificant.
The pharmaceutical development has been described in sufficient detail.

Manufacturing process
The film-coated tablets are manufactured using a standard process: mixing, lubricating, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. requirements or USP/NF requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units (content uniformity), related substances, assay and microbial limits. The shelf-life and release requirements are identical. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on twelve commercial-scale batches stored at 25°C/60% RH (60 months) and four commercial-scale batches stored at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVDC-Aluminium blisters. No significant changes are seen in the stability studies. The proposed shelf-life of 60 months is justified. A photostability study demonstrated that the product is not sensitive to light. Changes were seen at higher temperatures and humidity; therefore, the applicable storage condition is ‘do not store above 30ºC, protect from moisture’.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is from animal origin (derived from healthy animals). All other excipients are not of human or animal origin, so a theoretical risk of transmitting TSE can be excluded.

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

Bioequivalence/ Waiver

In order to obtain a biowaiver, the following rationale was provided: the originator has confirmed that this product is produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as their currently manufactured reference product.

The member states have been ensured that Letrozol Sandoz 2.5 mg is qualitatively and quantitatively equivalent to the reference product Femara, and have therefore granted a biowaiver.

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 MAH made a commitment to amend the SPC, PIL and labelling according to the Commission Decision of the reference product Femara (currently under Article 30(2) Referral) by variation. The variation will be submitted after finalisation of the Referral.

Readability test

The package leaflet has not been evaluated via a user consultation study. The MAH submitted a bridging report, showing that the content and lay-out of the PIL in full accordance with the innovator's (Femara, FR/H/0110/001/II/046). No separate user test is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Letrozol Sandoz 2.5 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is 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.

The MAH did not submit a bioequivalence study, but provided sufficient information to demonstrate that the product is quantitatively and qualitatively similar to Femara and is produced in the same manufacturing site..

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other letrozole containing products.

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

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 Sandoz 2.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 September 2010. Letrozol Sandoz 2.5 mg, film-coated tablets was authorised in the Netherlands on 2 November 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 September 2010 to October 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 13 October 2013.

The following post-approval commitment has been made during the procedure:

<u>Product information</u>

- The MAH committed to submit a variation in order to harmonise SPC following the outcome of the article 30 referral for originator product Femara.

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