CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Letrozol Astron 2.5 mg film-coated tablets
Astron Research Limited, 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/1383/001/DC
Registration number in the Netherlands: RVG 102441

30 November 2009

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:	4 August 2009
Concerned Member States:	Decentralised procedure with AT, BE, DE, DK, EL, ES, FI, FR, IE, IT, NO, PT, SE
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 Astron 2.5 mg film-coated tablets, from Astron Research Limited. The date of authorisation was on 4 August 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. 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 Tablets 2.5 mg, registered in Germany. 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 CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacturing process
Letrozol is prepared from an in-house starting material via a one-step synthesis followed by a purification step. The drug substance specification includes adequate limits for this solvent and for all other solvents used during synthesis. 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 specification is in line with the CEP, with additional requirements for particle size. Batch analytical data demonstrating compliance with the drug substance specification were provided for three commercial-scale batches.

Stability
The active substance is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *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 Astron 2.5 mg are yellow, round, biconvex, film-coated tablets, plain on both sides.

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

The excipients are:
Tablet core - lactose monohydrate, maize starch, hypromellose (E464), cellulose microcrystalline (E460), sodium starch glycolate, colloidal anhydrous silica (E551), magnesium stearate (E572).

Coating (Opadry 03B82927 yellow)- hypromellose (E464), titanium dioxide (E171), iron oxide yellow (E172), macrogol, talc (E553b).

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 are also present in the innovator product. Development focused on the manufacturing process for which a wet granulation approach was finally chosen. The choice of the manufacturing process is justified. The packaging is usual and suitable for the product at issue. The pharmaceutical development of the product was adequately performed.

Dissolution
A pilot-scale batch was used for the bioequivalence studies. It was compared to a German reference product. More than 85% of the generic and the reference product were dissolved in all tested media after 15 minutes indicating that the dissolution profiles are similar.

Manufacturing process
The manufacturing process involves wet granulation of Letrozole and some excipients followed by compression of the total blend and film-coating. The manufacturing process was adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product was presented for three pilot-scale batches among which the batch used in the bioequivalence study. Process validation for full scaled batches will be performed post authorisation.

Quality control of drug product
The product specification for the tablets includes tests for appearance, average weight, identity, dissolution, related substances, assay, content uniformity, microbial limits, identification of titanium dioxide, and identification of iron oxide yellow, and loss of water. The release and end of shelf life requirements are identical and considered acceptable.
The analytical methods were adequately described and validated. Batch analysis data from the proposed production site were provided for three pilot-scale batches demonstrating compliance with the release specification. A commitment was made to submit batch analytical data of three commercial-scale batches.

Stability tests on the finished product
Stability data on the product was provided for three pilot-scale batches stored at 25°C/60% RH (24 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 packaged in the commercial packaging. Except for a slight increase in loss on drying at long term conditions, 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 36 months could be granted. No special storage conditions are required. The MAH committed to submit long term and accelerated stability data of the first three commercial scale batches, at least up to the claimed shelf life of 36 months.

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 Letrozol Astron 2.5 mg film-coated tablets (Astron Research Limited, UK) is compared with the pharmacokinetic profile of the reference product Femara 2.5 mg tablets (Novartis Pharma GmbH, Germany).

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, open-label, balanced, randomised, two-treatment, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects. Mean age was 25 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 28 days, but not more than 35 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 24, 48, 72, 96, 144, 192 and 240 hours after administration of the products.

Analytical/statistical methods
Letrozole should not be used in pre-menopausal women, therefore, the choice for male subjects is acceptable. The analytical method is adequately validated and 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
Twenty-three of the 32 subjects completed both phases of the trial according to the conditions laid out in the protocol. One subject was withdrawn from the study during the first period because he missed several sampling times, 2 subjects were withdrawn at the second period because of medical grounds, 3 subjects discontinued from the trial on their own record, and 1 subject was withdrawn because of a positive alcohol test. The 23 remaining volunteers 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=23	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1889 ± 796	2008 ± 885	38.1 ± 5.7	2.0 (1.0-8.0)	44 ± 16
Reference	1851 ± 753	1963 ± 857	35.1 ± 7.4	2.5 (0.75-8)	45 ± 19
***Ratio (90% CI)**	1.01 (0.97 - 1.05)	1.00 (0.96 - 1.03)	1.10 (1.02 - 1.18)	-	-
CV (%)	8	7	14	-	-

$AUC_{0-\infty}$ 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 Astron 2.5 mg film-coated tablets 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

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 two rounds. No weaknesses to the PIL were identified, and the criterion for success was met easily. However, it must be noted that the questions asked were of a very simple nature. Therefore, it is not entirely clear how well the information in the PIL was understood, or how well it can be used by the respondents.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Letrozol Astron 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.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Letrozol Astron 2.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 February 2009. Letrozol Astron 2.5 mg film-coated tablets was authorised in the Netherlands on 4 August 2009.

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 registration to October 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 June 2012.

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

Quality - medicinal product

- The MAH committed to perform process validation on the first 3 commercial-scale batches.
- The MAH committed to submit batch analytical data of commercial-scale batches.
- The MAH committed to place the first 3 commercial-scale batches on long term stability studies through the proposed shelf life and on accelerated studies for six months.

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 to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; not including batch control/testing.	NL/H/1383/ 001/IA/001	IA	17-4-2009	1-5-2009	Approval	N