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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Anastrozol SUN 1 mg, film-coated tablets
Sun Pharmaceutical Industries Europe B.V., the Netherlands

anastrozole

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/1795/001/DC
Registration number in the Netherlands: RVG 105752

28 October 2010

Pharmacotherapeutic group:	hormone antagonists and related agents; enzyme inhibitors
ATC code:	L02BG03
Route of administration:	oral
Therapeutic indication:	treatment of advanced breast cancer in postmenopausal women, adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer, and adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.
Prescription status:	prescription only
Date of authorisation in NL:	20 October 2010
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, 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 Anastrozol SUN 1 mg, film-coated tablets from Sun Pharmaceutical Industries Europe B.V. The date of authorisation was on 20 October 2010 in the Netherlands.

The product is indicated for:

- Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.
- Adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer.
- Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

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

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, oestradiol is produced primarily by the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues. Oestrone is subsequently converted to oestradiol. Lowering circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Arimidex film-coated tablets 1 mg which has been registered in the United Kingdom by AstraZeneca UK Limited since August 1995. In the Netherlands the reference product has been registered since 5 September 1996 under NL License RVG 19123. In addition, reference is made to Arimidex 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 Arimidex film-coated tablets 1 mg, registered in the UK. 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 anastrozole, an established active substance, described in the Pharmacopoeia of the United States (USP*). The active substance is a white to off-white powder, which is freely soluble in methanol and practically insoluble in water. The active substance does not have chiral centra. It exists as two polymorphic forms (form I and II). Polymorphic form I is used.

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 drug substance is manufactured in two reaction steps. The elucidation of structure and the identification of impurities have been adequately characterized. The specifications of the other used materials are acceptable.

Quality control of drug substance
The active substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. The substance is compliant with the USP monograph. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 pilot-scale batches stored at 30°/65% RH (3 years) and 40°C/75% RH (6 months), and 3 commercial-scale batches stored at 25°/60% RH (9 months) and 40°C/75% RH (6 months). The active substance remains stable under all conditions. Furthermore, de active substance was shown to be photostable. The proposed re-test period of 3 years is justified.

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

Medicinal Product

Composition
Anastrozol SUN is a white to off white circular, biconvex, film-coated tablet debossed with "A1" on one side.

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

The excipients are:
Core - lactose monohydrate, povidone (E1201), sodium starch glycolate type A, magnesium stearate (E572).

Coating – Opadry white (hypromellose (E464), titanium dioxide (E171), polyethylene glycol 400).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator. The goal was to develop a film-coated tablet that was essentially similar to the innovators product Arimidex® 1 mg. The manufacture and composition of the bio-batches used in bioequivalence study is identical to the marketed product. The product rapidly dissolute in three buffers (>80% in 15 minutes) and the dissolution profiles of the biobatch and the reference batch are comparable. The tablet cores have a completely identical composition and only minor differences in the film coat are observed (macrogol 400 is used instead of macrogol 300 and there are small quantitative differences for the other components).
The pharmaceutical development of the product has been adequately performed

Manufacturing process
The tablets are produced in three stages. First a base granulate is produced, the granules are dried and screened, then the active substance and other excipients are mixed. This mixture is blended with the granules and finally the blend is compressed into core tablets, followed by coating of the core tablets. Process validation data on the product has been presented for 3 pilot-scale batches. The product is manufactured using conventional manufacturing techniques, but is considered non-standard, based on the total amount of active substance in the drug product (< 2%). The validated batch size will be regarded as the maximum batch size until further validation data are presented.
The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, dissolution, assay, degradation, water, uniformity of dosage units, and microbial contamination. All test parameters are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 3 commercial-scale batches stored at 25°C/60% RH (12 months) and 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/Al blisters.
No changes are seen under both conditions. Also, results of photostability studies were provided. No changes are observed when compared with the unexposed product. The tablet is considered to be photostable. In view of the requirements stated in the ICH guideline, a shelf life of 2 years and no special storage condition was granted for the tablets packed in PVC/Al blisters.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin that is used in the current drug product. The necessary declarations with respect to the TSE safety of lactose were provided.

II.2 Non-clinical aspects

This product is a generic formulation of Arimidex, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone pre-clinical 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 anastrozole 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

Anastrozol 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 Anastrozol SUN 1 mg (Sun Pharmaceutical Industries, the Netherlands) is compared with the pharmacokinetic profile of the reference product Arimidex 1 mg tablets (AstraZeneca Limited, UK).

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, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy female subjects. Healthy surgically sterile female subjects between 18-55 years of age or healthy postmenopausal female subjects between 35-55 years of age were included. Each subject received a single dose (1 mg) of one of the 2 anastrozole formulations. There were 2 dosing periods, separated by a washout period of 25 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 48, 72, 120, 168 and 216 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
Four subjects were not dosed in the second period: one subject was withdrawn due to vomiting 1.5 hours after drug administration in period 1. Another subject dropped out without a specific reason in period 1 during blood sampling. A third volunteer was withdrawn due to a dog bite requiring concomitant medication during the washout period and one subject was withdrawn due to an adverse event (significant pre-study haematology report) in period II.
Overall, the statistical analysis set consisted of 22 healthy female subjects who ranged in age from 36 to 55 years, with a mean age of 48.2 years. Mean body weight for all subjects was 53.2 kg with a range of 50 to 64 kg.

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

Treatment N=22	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	964 ± 236	1042 ± 296	21.1 ± 2.8	1.25 (0.75-2.00)	51 ± 14
Reference	978 ± 257	1057 ± 306	20.8 ± 3.0	1.25 (0.75-2.00)	50 ± 12

***Ratio (90% CI)**	0.99 (0.95-1.04)	--	1.02 (0.98-1.07)	--	--
CV (%)	8.6	--	8.7	--	--

$AUC_{0-\infty}$ 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} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. AUC_{0-t} was at least 80% of $AUC_{0-\infty}$ for all subjects. Based on the pharmacokinetic parameters of anastrozole under fasted conditions, it can be concluded that Anastrozol SUN 1 mg and Arimidex 1 mg tables are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Anastrozole should be taken once daily without reference to food intake. Therefore, 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

Anastrozole was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of anastrozole 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 content of the SPC approved during the decentralised procedure is in accordance with those for other anastrozole products. Arimidex appears in the CMD(h) list of medicinal products selected for harmonisation of the SPC via a referral procedure under Article 30(2) of Directive 2001/83/EC. After finalization of the SPC harmonisation procedure for Arimidex, the texts of Anastrozol SUN 1 mg will be updated accordingly.

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, followed by two rounds with 10 participants each. The selected participants represented the target patient population: females, aged 45 years and over. The questionnaire consisted of fifteen questions covering relevant safety issues of the product.

Two additional questions on the layout, design, font and overall readability (patient friendliness) of the leaflet were also included in the questionnaire. During the pilot test, the leaflet was reviewed and the layout and readability was improved. The leaflet was not further amended between rounds one and two.

According to the results, 18 out of 20 participants (90%) were able to find the information for every question and to understand that information correctly.
Comments made by the participants indicated that the leaflet is easy to navigate and that the information is easy to find and to understand. Recommendations for further improvement were also provided.
The results were in general well presented and documented. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Anastrozol SUN 1 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Arimidex film-coated tablets 1 mg. Arimidex 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 anastrozole 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 Anastrozol SUN 1 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 27 August 2010. Anastrozol SUN 1 mg, film-coated tablets was authorised in the Netherlands on 20 October 2010.

A European harmonised birth date has been allocated (11 August 1995) and subsequently the first data lock point for anastrozole is August 2012. The first PSUR will cover the period from August 2010 to August 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: April 2013.

There were no post-approval commitments made during the procedure.

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