CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nateran 25 mg, film-coated tablets Synthon B.V., the Netherlands

exemestane

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/1940/001/DC
Registration number in the Netherlands: RVG 106695

7 February 2011

Pharmacotherapeutic group:	hormone antagonists and related agents, enzyme inhibitors
ATC code:	L02BG06
Route of administration:	oral
Therapeutic indication:	adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2-3 years of initial adjuvant tamoxifen therapy; treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy
Prescription status:	prescription only
Date of authorisation in NL:	12 January 2011
Concerned Member States:	Decentralised procedure with BE, CZ, DE, EE, EL, ES, FI, FR, HU, IT, LT, LV, RO, SK, 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 Nateran 25 mg, film-coated tablets from Synthon B.V. The date of authorisation was on 12 January 2011 in the Netherlands.

The product is indicated for:

- adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy.
- treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.

Efficacy has not been demonstrated in patients with oestrogen receptor negative status.
A comprehensive description of the indications and posology is given in the SPC.

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, exemestane p.o. significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%. Exemestane does not possess any progestogenic or oestrogenic activity.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aromasin 25 mg coated tablets which has been registered in the UK by Pharmacia group since 16 December 1998. In the Netherlands, Aromasin 25 mg (NL License RVG 24443) has been registered through MRP UK/H/0326/001 by Pfizer BV since 19 October 1999. In addition, reference is made to Aromasin authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) 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 Aromasin 25 mg tablets, registered in the EEA and obtained from the German market. 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 exemestane, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to off-white powder and is readily soluble in dichloromethane, acetone and acetonitrile, partially soluble in ethanol, and practically insoluble in water. No polymorph forms have been detected. The molecule contains five chiral centers.

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 has been adequately described. No heavy metal catalysts or class I solvents are used in the synthesis. The active substance has been adequately characterized and acceptable specifications have been adopted for the solvents and reagents.

Quality control of drug substance
Adequate specifications are applied for the drug substance. General tests are performed in accordance with Ph.Eur. and the methods for identification, assay, related substances and residual solvents are developed in-house conducts. The specifications are 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 production-scale batches.

Stability of drug substance
The stability data on the active substance provided covers 36 months long-term, 12 months intermediate and 6 months accelerated storage conditions. After 6 months of accelerated storage, out-of-specification results were found. Based on the results, the claimed retest period of 27 months when stored in the original packaging below 30°C can be granted.

** 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
Nateran contains as active substance 25 mg of exemestane and is a yellow film-coated biconvex round tablet, debossed with 'E9MT' on one side and '25' on the other side.

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

The excipients are:
Core – mannitol (E421), hypromellose, crospovidone, polysorbate 80, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, colloidal anhydrous silica.

Coating – carmellose sodium (E466), maltodextrin, glucose monohydrate, titanium dioxide (E171), stearic acid (E570), 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 formulation and manufacturing process development have been described adequately. Comparative dissolution testing was performed with pilot-scale batches against the innovator product. In different pH buffers, the profiles can be considered similar with more than 85% dissolved after 15 minutes. The choice of manufacturing process and packaging material is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by wet granulation and is initiated by granulating. The granulate is dried, mixed with a number of excipients and lubricated. The blend is then compressed, coated and packed. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for three minimum batch size range batches.
The MAH committed to validate the first three batches of maximum scale.

Control of excipients
The excipients comply with the Ph.Eur. and Directive 95/45/EC. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, water content, hardness, uniformity of dosage units, identification (exemestane and colouring agents), dissolution, related substances, assay and microbiological quality. The release and shelf-life specifications are identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three minimum batch size batches as used for process validation stored at 25°C/60%RH (18 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/PVdC-Alu blisters. After 6 months of accelerated storage, an increase in impurities and a decrease in dissolution are observed. After 18 months of long-term storage, an increase in impurities and water content could be observed. Some variation was observed for assay values. However, all results remained within limits. The proposed shelf-life of 30 months could therefore be granted. The claimed storage condition ‘No special storage conditions’ is justified.
The MAH committed to reduce the shelf life in case out-of-specifications are detected prior to this time point in the long-term stability studies through the proposed shelf-life of 30 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Aromasin, 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 exemestane 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

Exemestane 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 Nateran 25 mg film-coated tablets (Synthon B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Aromasin 25 mg tablets (Pfizer Italia S.r.L), registered in the EEA and obtained from the German market.

The choice of the reference product
The choice of the reference is acceptable, as the product has been registered through an MRP and is considered to be identical in different countries. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, four-period, two-treatment, two-sequence, replicate design crossover bioequivalence study was carried out under fed conditions in 56 healthy post-menopausal female subjects, aged 47-74 years. Each subject received a single dose (25 mg) of one of the 2 exemestane formulations. The tablet was orally administered with 240 ml water after a 10 hour fasting period and after completely consuming a standardised breakfast. There were 4 dosing periods, separated by a washout period of 7 days. Subjects remained sitting in upright posture for the first 4 hours after the oral administration. Thereafter, the subjects were allowed to walk around freely within the facility. They refrained from drinking water 1 hour before until 1 hour after dosing in each period, except for the water given with medicine administration.

Blood samples were collected pre-dose and at 0.33, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.17, 2.33, 2.5, 2.67, 3, 4, 6, 8, 10, 12, 16, 24 and 36 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
Fifty-four subjects completed both periods and were included in statistical analysis. One subject voluntarily withdrew due to family emergency during the washout period prior to Period III. The other subject was dismissed by the investigator in study period II due to adverse effects.

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

Treatment N=54	**AUC_{0-36}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	54.9 ± 18.1	59.1 ± 18.3	24.7 ± 10.7	1.55 (0.50 – 3.00)	8.01 ± 3.14
Reference	53.2 ± 18.2	57.5 ± 18.8	25.0 ± 13.3	1.63 (0.50 – 4.00)	7.77 ± 3.33
***Ratio (90% CI)**	1.04 (1.01-1.07)	1.03 (1.01-1.06)	1.00 (0.94-1.07)	-	-

Intra-subject CV (%)	**Test**	12.7	12.5	28.5	32.9	33.0
	Reference	12.8	12.7	30.8	33.8	41.7

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ 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 exemestane under fed conditions, it can be concluded that Nateran 25 mg and Aromasin 25 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 AUC_{0-t} was greater than 80% of the $AUC_{inf,}$ except in 4 cases (2 with test and 2 with reference products). As absorption of exemestane is rapid, C_{max} is obtained at approximately 1.5 hours, this has no consequences for the conclusion of equivalence.
The conduct of a replicate design study was initiated by the high reported intraindividual variability for exemestane C_{max}. The intrasubject variability of C_{max} was indeed much higher (31%) than the intrasubject variability for $AUC_{0-\infty}$ (13%). Nevertheless, the calculated 90% CI for AUC_{0-t} and C_{max} for exemestane are within the 0.80-1.25 acceptance range.

Safety
No serious adverse events were reported during the conduct of this study. Fifty-four mild adverse events were observed in 27 subjects, such as hypotension, headache, vessel puncture site bruise, diarrhoea, anorexia, nausea, myalgia, dizziness, joint swelling, fatigue, catheter site oedema, catheter site bruise, catheter site pain and catheter site erythema. The safety issues were adequately addressed.

Concomitant intake with food increases the bioavailability of exemestane by 40%. In the SPC it is recommended to take the tablets once a day, after a meal. A bioequivalence study under fed conditions is in agreement with the Guideline on 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
Exemestane was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of exemestane 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. 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 that accepted for the reference product Aromasin.

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. A total of 16 questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nateran 25 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic forms of Aromasin 25 mg tablets. Aromasin 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 will ensure that systems and services are in place for compliance with their pharmacovigilance obligations; one commitment was made (see below).

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other exemestane 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 Nateran 25 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 December 2010. Nateran 25 mg, film-coated tablets was authorised in the Netherlands on 12 January 2011.

A European harmonised birth date has been allocated (16 December 1998) and subsequently the first data lock point for exemestane is December 2013. The first PSUR will cover the period from December 2010 to December 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: December 2015.

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

<u>Quality - medicinal product</u>
- The MAH committed to validate the first three batches of maximum scale.
- The MAH committed to reduce the shelf life in case out-of-specifications are detected prior to this time point in the long-term stability studies through the proposed shelf-life.

<u>Pharmacovigilance system</u>
- The MAH committed to fulfil the requirements of the pharmacovigilance system before the product is placed on the market.

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