CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Exemedica 25 mg film-coated tablets Regiomedica GmbH, Germany

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/1950/001/DC
Registration number in the Netherlands: RVG 106972

14 April 2011

Pharmacotherapeutic group:	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:	4 February 2011
Concerned Member State:	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 Exmestaan Regiomedica 25 mg film-coated tablets, from Regiomedica GmbH. The date of authorisation was on 4 February 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. A slight androgenic activity, probably due to the 17-hydro derivative, has been observed mainly at high doses. In multiple daily doses trials, exemestane had no detectable effects on adrenal biosynthesis of cortisol or aldosterone, measured before or after ACTH challenge, thus demonstrating its selectivity with regard to the other enzymes involved in the steroidogenic pathway.

Glucocorticoid or mineralocorticoid replacements are therefore not needed. A non dose-dependent slight increase in serum LH and FSH levels has been observed even at low doses: this effect is, however, expected for the pharmacological class and is probably the result of feedback at the pituitary level due to the reduction in oestrogen levels that stimulate the pituitary secretion of gonadotropins also in postmenopausal women.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aromasine 25 mg film-coated tablets (NL license RVG 24443) which has been registered in the UK by Pharmacia GmbH (member of Pfizer Group) since 1998 (original product). In the Netherlands, Aromasine has been registered since 1999 by the Pfizer B.V., the Netherlands.
In addition, reference is made to Aromasine 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Exemestane 25 mg tablets, registered in France. 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 generic medicinal products.

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
Exemestane is an established active substance which is not described in any pharmacopoeia*. The active substance is insoluble in water. It exhibits polymorphism. There are no stereo isomers.

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.

Manufacture
The manufacturing process consists of four steps. No class I organic solvents are used. No metal catalysts are involved. The active substance was adequately characterized by the ASMF holder and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification was established in house by the MAH. It differs from the drug substance specification of the ASMF holder with regard to the limits of the specified impurities, the particle size limit, and the method for determination of the polymorphic form. The drug substance specification is regarded to be acceptable in view of the route of synthesis and various European guidelines.Batch analytical data demonstrating compliance with the drug substance specification were provided for three production scale batches.

Stability of drug substance
Stability data were provided for five production scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). Three batches were milled and two were un-milled. The batches were stored in a simulated marketing package. No specific trends or significant changes were observed. The proposed re-test period of 24 months with no specific storage condition if stored in the proposed container closure system is justified.
The MAH has committed to put the first three production batches of the drug substance on long-term stability studies throughout the proposed re-test period.

** Pharmacopoiea are official handbooks in which methods of analysis with specifications for substances are laid down by the authorities.*

Medicinal Product

Composition
Exemedica 25 mg are round, biconvex, white to off-white, bevel-edged film-coated tablets marked with an "*E*" on one side.

The excipients are:
Tablet core: mannitol, crospovidone, hypromellose, sodium starch glycolat (type A), polysorbate 80, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silicia.
Film-coating: hyromellose, titanium dioxide (E171), macrogol 400.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Formulation development included exemestane particle size, level of excipients, method of excipient addition and tablet coating development. The drug substance needs to be micronized to achieve a suitable dissolution rate. Moreover, a surfactant needs to be added to the dissolution medium to obtain sink conditions. Due to the poor flow characteristics of micronized exemestane, a wet granulation approach was selected. The choices for manufacturing process and packaging are justified.
Composition and manufacturing process of the generic batch used in the bioequivalence study correspond to those proposed for commercial production. Dissolution of the biobatches is similar in 0.25% SLS and visually comparable in pH 1.2 HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. In the latter three media, no sink conditions are achieved. The reference product from the FR market was shown to be representative by comparing its dissolution profile to several batches taken from various European markets. The impurity profiles of the generic and reference product are comparable.
Pharmaceutical development of the product was adequately performed. From a chemical pharmaceutical point of view, the generic and the reference product are considered to be similar.

Container closure system
The container closure system is a blister system comprising of a clear PVC film (250 µm) coated uniformly with PVDC on the inner side (120 g/m^2) and a backing of aluminium foil (20 µm) with heat seal lacquer. The blister strips are enclosed in an outer carton. Stability studies confirm the suitability of the container closure system.
Specifications were provided for both foils. They include tests for description, identity (plastics and heat seal lacquer by IR, aluminium by precipitation), dimensions, and a check of the *Certificate of Conformity of the supplier*. Sample IR scans were provided. Example Certificates of Analysis of both foils were included.
The PVC/PVDC foil complies with the requirements of the European Pharmacopoeia and with Directive 2002/72/EC.

Manufacturing process
The manufacturing process involves wet granulation, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product was presented for production scale batches of the lower proposed batch size. Full-scale batches will be validated according to the same protocol.

Excipients
With the exception of the coating premix, all excipients are of pharmacopoeial grade. The specifications of the excipients are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of exemestane by HPLC and UV-PDA, identification of titanium dioxide, resistance to crushing, thickness, diameter, average tablet mass, assay, uniformity of dosage units, related substances, dissolution, and microbial limits. The release and shelf-life limits differ with regard to the limits for the specified impurities and the limit for total impurities. The limits for the specified impurities are in line with the qualification threshold of 0.5% at the end of shelf-life. The specification is considered acceptable. Not all tests are performed during stability studies, this is

considered acceptable. The analytical methods were adequately described and validated. Batch analytical data were provided on three batches of the lower proposed batch size from a specific manufacturing site as well as from two batches of another specific manufacturing site (commercial manufacturing site) demonstrating compliance with the release specification.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. For the purpose of microbiological quality, the drug product is classified as a non-aqueous oral preparation. The specifications for Total Aerobic Microbial Count, Total Yeasts and Moulds Count, and *Escherichia Coli* have been established in line with the requirements of the harmonised Ph. Eur./USP/JP monograph for Microbiological Quality (Ph. Eur. 5.1.4).

Stability tests on the finished product
Stability data on the product has been provided for three batches of the lower proposed batch size from one site and for two batches of the other site stored at 25°C/60% RH (24 months / 6 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 Al-PVC/PVDC blisters. No significant changes were observed. At both storage conditions, increasing trends were observed for resistance to crushing and average mass. Impurity levels only increased at accelerated conditions. The levels of specified impurities remained fairly constant while unspecified impurities increased. On the basis of the provided stability data, the proposed shelf-life of 30 months is justified. The drug product does not need specific storage conditions. It is photostable. Additional stability data for the batches of one specific site are needed to fully support the claimed shelf-life and storage conditions.
The MAH has committed to continue the stability studies for the batches manufactured at one specific site to the proposed shelf-life. In addition, the MAH has committed to continue the stability studies up to the proposed shelf-life (36 months) for all batches manufactured at another specific site and any out of specification results will be reported to the authorities.

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.

II.2 Non clinical aspects

This product is a generic formulation of Aromasine, 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 one bioequivalence study in which the pharmacokinetic profile of the test product Exemedica 25 mg film-coated tablets (Regiomedica GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Aromasine 25 mg tablets (Pfizer Italia S.r.l., France).

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 (if applicable) in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Study design
A monocentre, single-dose, randomised, open-label, two-treatment, two-way crossover bioequivalence study was carried out under fed conditions in 110 healthy male volunteers, aged 22-55 years. Both smokers (no more than 9 cigarettes per day) and non-smokers were involved. 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 at least 10 hours of fasting and after completely consuming a standardised moderate fat breakfast (650 kilocalories). Subjects were required to remain seated and avoid lying down or sleeping (unless medically necessary, procedurally required, or to go to the bathroom) for the first 4 hours after dosing in each period. Subjects were fasted for at least 4 hours after the oral administration. Subjects were served a controlled meal after 4 hours post dose, and at appropriate times thereafter, in each period. They refrained from drinking water 1 hour before until 1 hour after dosing in each period (except for the water given with the medicine administration).
There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours after administration of the products.
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
There were 100 subjects enrolled in the main study (Group 1) according to the protocol. However, due to the unexpected large number of drop-outs, a protocol amendment, dated May 27, 2009, was required in order to include additional subjects (Group 2).
As per protocol, in the event that the number of drop-outs exceeds initial expectations, subjects who withdraw or are withdrawn might be replaced. Therefore, as the withdrawal rate was high during the main part of this study (Group 1), a replacement study including 10 additional subjects (Group 2) was performed to ensure to have the initial expected statistical power. The same design and the same procedures were used for both groups.
Ten subjects withdrew from Group 1 in period I, in which five of them were withdrawn due to personal reasons, two subjects were due to the possibility of non-compliance, two subjects were due to adverse effects, and one was withdrawn due to inappropriate behaviour. In Group 2, 2 subjects were withdrawn due to absence of confinement for Period 2.
Eighty-six subjects completed all the periods, in which four subjects missed at least two adjacent return visits from 36.0- to 120-hour post-dose in Periods 1 or 2. The pharmacokinetic profile of these subjects could not be adequately characterised, therefore, they were excluded in statistical analysis.
A total of 82 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N = 82	**AUC_{0-144}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	61.1 ± 23.5	71.0 ± 25.9	23.5 ± 15.4	1.25 (0.33 – 4.00)	18.05±12.0
Reference	62.0 ± 26.0	71.6 ± 28.6	24.4 ± 15.2	1.25 (0.50 – 3.00)	17.8±10.2
***Ratio (90% CI)**	1.00 (0.96 – 1.04)	1.01 (0.96 – 1.06)	0.96 (0.88 – 1.06)	---	---
CV (%)	15.5	17.3	36.5	---	---

$AUC_{0-\infty}$ 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 (active substance) under fed conditions, it can be concluded that (test) and the (reference) are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
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.

Adverse events
No deaths or serious adverse events were reported during this study. A total of 51 treatment-emergent adverse events (TEAEs) were reported by 31 of the 98 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 26 TEAEs reported by 19.8% (n=18) of the 91 subjects who received test product and 25 TEAEs reported by 18.3% (n=17) of the 93 subjects who received reference product.
TEAEs occurred among treated subjects were: somnolence (major), inject site react (major), hypertens, dry mouth, asthenia, hyperglycemia, hematuria, leucopenia, creatinine inc, SGPT inc, albuminuria, dizziness, pain, edema, infect, myalgia, nausea, anxiety, hallucin, amblyopia and euphoria.

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 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 revised according to comments from the Member states. The proposed SPC is approvable.

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 5 participants and a main test with 20 participants divided in 2 rounds. The selected participants were women between 47 and 83 years of age, representing the target population for this medicinal product. The selection of participants is considered adequate.
The questionnaire consisted of 18 questions, 7 questions related to understanding the information and 11 questions related to locating and using the information properly. Suggestions of the participants on the layout, design and friendliness of the PL were also recorded. The questionnaire addresses the most relevant safety issues of the product.
The test was carried out by face-to-face interviews. The average duration of the interviews was relatively short: 18 minutes for the pilot test and 14 minutes for the main test.
A few modifications to the PL were made after the pilot test. Although not mentioned in the rapport, it is assumed that no amendments were made between rounds one and two. A marked version of the package leaflet indicating changes made during the readability test was provided.

According to the results, more that 90% of the participants were able to locate the information and more than 90% of them were able to understand the information correctly. More than 80% of the participants completed the task easily. The results are in general well presented and documented. The report is clear and concise. Good suggestions for improvement were provided.
The tested 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.

Conclusion
The results of the test indicate that the Package Leaflet for Exemestane 25 mg film coated tablets fulfils the requirements of readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Exemedica 25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Aromasine tablets. Aromasine 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.

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 Exemedica 25 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 January 2011. Exemedica 25 mg film-coated tablets is authorised in the Netherlands on 4 February 2011.

A European harmonised birth date has been allocated 16 December 1998 and subsequently the first data lock point for exemestane Decembner 2013. The first PSUR will cover the period from approval to February 2014, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 August 2014.

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

Quality - active substance
- The MAH has committed to put the first three production batches of the drug substance on long-term stability studies throughout the proposed re-test period.

Quality - medicinal product
- The MAH has committed to continue the stability studies for the batches manufactured at one specific site to the proposed shelf-life.
- The MAH has committed to continue the stability studies up to the proposed shelf-life (36 months) for all batches manufactured at one specific site and any out of specification results will be reported to the authorities.

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
TEAE	Treatment-Emergent Adverse Events
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