COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Exemestaan Pfizer, 25 mg coated tablets (exemestane)

NL/H/4753/001/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Exemestaan Pfizer, 25 mg coated tablets. The procedure was finalised in the United Kingdom (UK/H/4519/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

EXEMESTANE 25 MG COATED TABLETS

UK/H/4519/01/DC

UK Licence No: PL 00057/1202

PFIZER LIMITED

LAY SUMMARY

Exemestane 25 mg coated tablets

(Exemestane, coated, tablet, 25 mg)

This is a summary of the Public Assessment Report (PAR) for Exemestane 25 mg coated tablets (PL 00057/1202). It explains how Exemestane 25 mg coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Exemestane 25 mg coated tablets.

For practical information about using Exemestane 25 mg coated tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Exemestane 25 mg coated tablets and what are they used for?

Exemestane 25 mg coated tablets are used to treat:

1. hormone dependent early breast cancer in postmenopausal women after they have completed 2-3 years of treatment with the medicine tamoxifen.

2. hormone dependent advanced breast cancer in postmenopausal women when a different hormonal drug treatment has not worked well enough.

The company (Pfizer Limited) that makes Aromasin 25 mg coated tablets (PL 00057/0930) has agreed that its scientific data can be used as a basis for the grant of identical licences for Exemestane 25 mg coated tablets.

How do Exemestane 25 mg coated tablets work?
Exemestane 25 mg coated tablets contain the active ingredient, exemestane which belongs to a group of medicines known as aromatase inhibitors. These drugs interfere with a substance called aromatase, which is needed to make the female sex hormones, oestrogens, especially in postmenopausal women.
Reduction in oestrogen levels in the body is a way of treating hormone dependent breast cancer.

How are Exemestane 25 mg coated tablets used?
The pharmaceutical form of this medicine is a coated tablet and the route of administration is oral (by mouth).

Exemestane 25 mg coated tablets should be taken after a meal at approximately the same time each day.

The usual dose in adults and the elderly is 25 mg tablet daily. This medicine is not suitable for use in children.

This medicine can only be obtained with a prescription.
Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Exemestane 25 mg coated tablets is used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Exemestane 25 mg coated tablets have been shown in studies?
Exemestane is considered identical to a previously authorised informed consent application Aromasin 25 mg coated tablets (PL 00057/0930), with the same benefits and risks. So, no new studies have been provided for Exemestane 25 mg coated tablets, but reference is made to the studies for Aromasin 25 mg coated tablets (PL 00057/0930).

What are the possible side effects from Exemestane 25 mg coated tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them. Exemestane 25 mg coated tablets is considered identical to a previously authorised informed consent application Aromasin 25 mg coated tablets (PL 00057/0930), with the same benefits and risks.

For a full list of all the side effects reported with Exemestane 25 mg coated tablets see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why was Exemestane 25 mg coated tablets approved?
The MHRA decided that the benefits of Exemestane 25 mg coated tablets are greater than the risks and recommended it is approved for use.

What measures are being taken to ensure the safe and effective use of Exemestane 25 mg coated tablets?
Safety information has been included in the Summaries of Product Characteristics and the package leaflet for Exemestane 25 mg coated tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Exemestane 25 mg coated tablets
A Marketing Authorisation was granted in the UK on 06 May 2011.
The full PAR for Exemestane 25 mg coated tablets follows this summary.

For more information about treatment with Exemestane 25 mg coated tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2018.

EXEMESTANE 25 MG COATED TABLETS
PL 00057/1202

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria (AT), Belgium (BE), Germany (DE), Denmark (DK), Greece (EL), Finland (FI), France (FR), Ireland (IE), Iceland (IS), Italy (IT), Luxembourg (LU), the Netherlands (NL), Sweden (SE) and the UK considered that the application for Exemestane 25 mg coated tablets could be approved.

Exemestane 25 mg coated tablets is a prescription only medicine (POM) and is indicated for the:

- adjuvant treatment of postmenopausal women with oestrogen receptor postitive invasive early breast cancer (EBC), 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.

This application is the same as Aromasin 25 mg coated tablets (PL 00057/0930; Pfizer Limited) which is already authorised.

This application for Exemestane 25 mg coated tablets were submitted according to Article 10c of Directive 2001/83/EC, as an informed consent application referring to data submitted for Aromasin 25 mg coated tablets (PL 00032/0236; UK/H/0326/001/) first authorised to Pharmacia Limited on 16 December 1998.

Exemestane is a potent, orally active, irreversible steroidal aromatase inactivator. Aromatase inhibitors are proven and established treatment options that selectively inhibit aromatase and decrease oestrogen in both the plasma and breast tumour tissue of hormone-receptor-positive postmenopausal women in order to help prevent recurrence of the tumour or to slow its growth sufficient to confer clinical benefits

No new data were submitted nor were they necessary for this informed consent application, as the data are identical to that of the previously granted Aromasin 25 mg coated tablets.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Following approval the MAH subsequently withdrew the product from the following CMS:

Belgium (BE), Denmark (DK), Spain (ES), Ireland (IE), Iceland (IS), Luxembourg (LU) and Sweden (SE).

II QUALITY ASPECTS

II.1 Introduction

These are abridged applications for for Exemestane 25 mg coated tablets (PL 00057/1202) submitted under Article 10c of Directive 2001/83/EC, as amended.

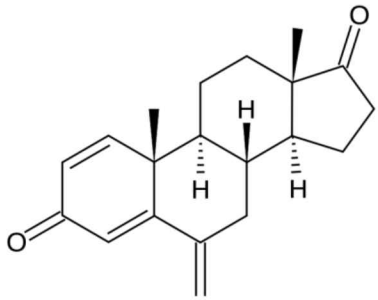
The application cross-refers to the refernce Aromasin 25 mg coated tablets (PL 00057/0930) which was authorised to the marketing authorisation holder (MAH) Pfizer Limited on 18 October 2012, following a change of authorisation from Pharmacia Limited (PL 00032/0236). Pharmacia Limited was granted a marketing authorisation for Aromasin 25mg coated tablets (PL 00032/0236) on 16 December 1998. The application is considered valid.

III.1 QUALITY ASPECTS

- **Active substance**

INN/Ph.Eur name: Exemestane
Chemical names: 6-methyleneandrosta-1,4-diene-3,17-dione

Structural formula:



Molecular formula: $C_{20}H_{24}O_2$

Appearance: White to slightly yellow crystalline powder
Solubility: insoluble in water, soluble in tetrahydrofuran, N, N-dimethylformamide, acetone, acetonitrile and methanol. Sparingly soluble in ethanol and slightly soluble in n-hexane.

Molecular weight: 296.4

The source of the active substance is in-line with the source of the active substance for Aromasin 25 mg coated tablets.

All aspects of the manufacture of the active substance from its starting materials, specification, container closure system and stability are identical to that of Aromasin 25 mg coated tablets.

II.2. Drug Substance

Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3. Medicinal Product

Name

The proposed product name for this application is Exemestane 25 mg coated tablets. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

This product is packaged in blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVDC) and aluminium. Pack sizes are 15, 20, 30, 90, 100 and 120 coated tablets.

The proposed shelf-life is 3 years with no special storage conditions.
This is consistent with the details registered for Aromasin 25 mg coated tablets.

Legal status

Prescription only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company

Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers

The manufacturing sites are consistent with those registered for Aromasin 25 mg coated tablets and evidence of GMP compliance has been provided.

Qualitative and quantitative compositions

The proposed compositions are consistent with the details registered for the cross-reference products.

Manufacturing process

The manufacturing process is consistent with the details registered for Aromasin 25 mg coated tablets and the maximum batch size for each product is stated.

Finished product/shelf-life specifications

The proposed finished product specifications are in line with the details registered for the cross-reference products.

TSE Compliance

The composition is consistent with the details registered for Aromasin 25 mg coated tablets.

None of the excipients used contain material of human origin. This is confirmed by a statement from the Quality Expert. A valid Transmissible Spongiform Encephalopathy (TSE) Certificate of Suitability has been provided from the supplier of the stearic acid.
This information is consistent with that for Aromasin 25 mg coated tablets.

Bioequivalence

No bioequivalence data are required to support these simple abridged applications because the proposed products are manufactured to the same formulae utilising the same processes as the cross-reference product, Aromasin 25 mg coated tablets (PL 00057/0930)

Expert Report

The applicant cross-refers to the data for Aromasin 25 mg coated tablets (PL 00057/0930) to which this application is claimed to be identical. This is acceptable.

Product Name and Appearance
See Section II.3 'Medicinal Product; Name' for details of the proposed product name. The appearance of the product is identical to that of the cross-reference product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The data submitted with the application is acceptable. The grant of Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

Introduction
As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

The pharmacodynamics, pharmacokinetics and toxicological properties of exemestane are well-known and exemestane is a widely used, well-known active substance. The applicant has not provided any new non-clinical data and none are required as this is an informed consent application, referring to data approved for Aromasin 25 mg coated tablets.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
A satisfactory justification has been submitted for the non submission of a Risk management plan.

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

V User consultation

The patient information leaflet has been prepared in-line with the details registered for the Aromasin 25 mg coated tablets. User testing results have been submitted for Aromasin 25 mg coated tablets (PL 00032/0236), together with a bridging report. This is satisfactory as the proposed PIL is identical with the exception of the product name. As the proposed PIL is in line with the Aromasin PIL the need for additional testing is not considered necessary.

The results of consultations with target patient groups ("user testing") are in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

The artwork is comparable to the artwork registered for Aromasin 25 mg coated tablets and complies with statutory requirements.

VI Overall conclusion, benefit/risk assessment and recommendation

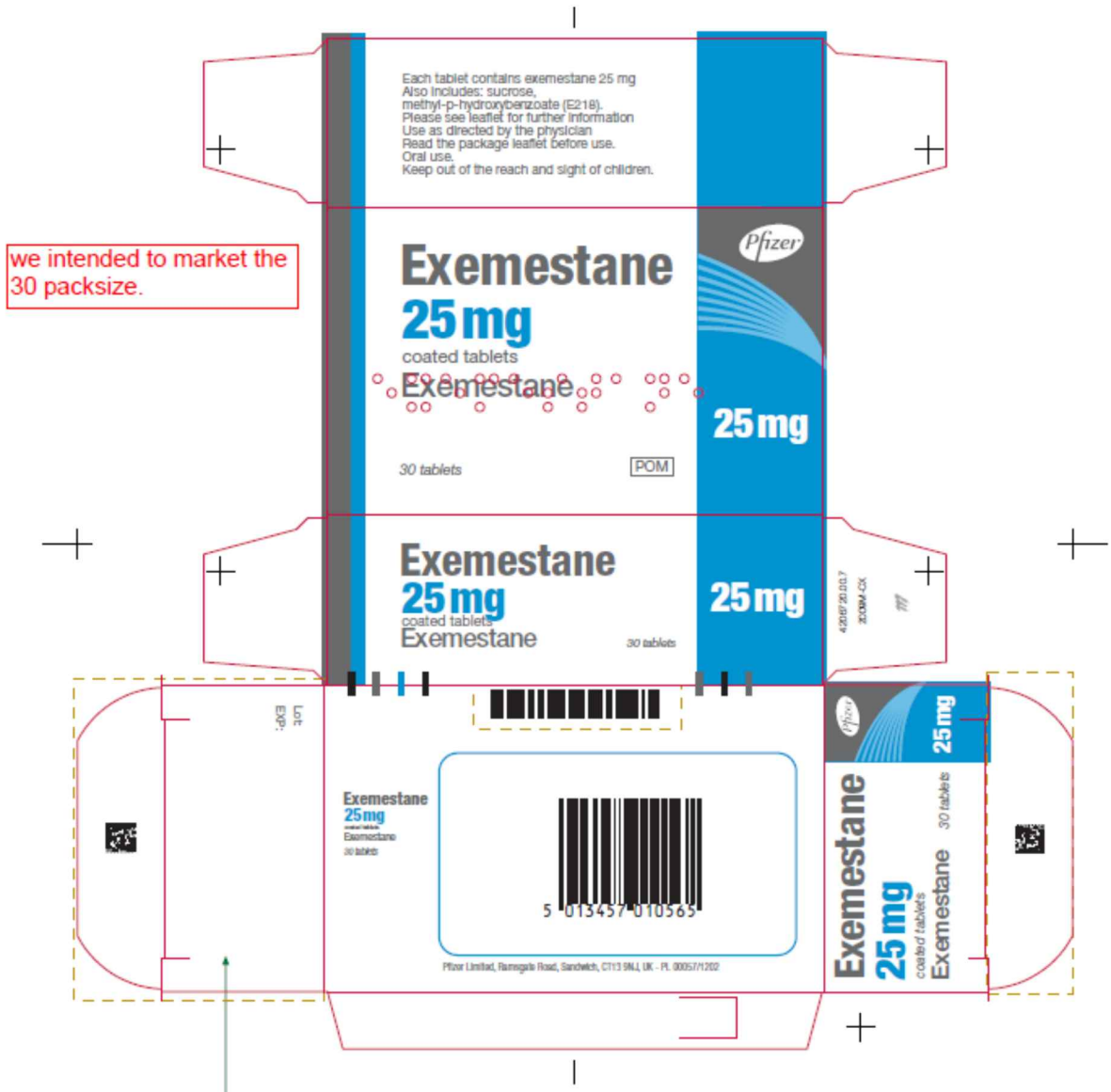
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with Exemestane is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The SmPC and PIL are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:


we intended to market the 30 packsize.
Each tablet contains exemestane 25 mg
Also includes: sucrose, methyl-p-hydroxybenzoate (E218).
Please see leaflet for further information
Use as directed by the physician
Read the package leaflet before use.
Oral use.
Keep out of the reach and sight of children.
Exemestane
25 mg
coated tablets
Exemestane
30 tablets
POM
25 mg
Exemestane
25 mg
coated tablets
Exemestane
30 tablets
25 mg
Lot:
EXP:
Exemestane
25 mg
Exemestane
5 013457 010565
Pfizer Limited, Ramsgate Road, Sandwich, CT13 9NJ, UK - PL 00057/1202
25 mg
Exemestane
25 mg
coated tablets
Exemestane
30 tablets
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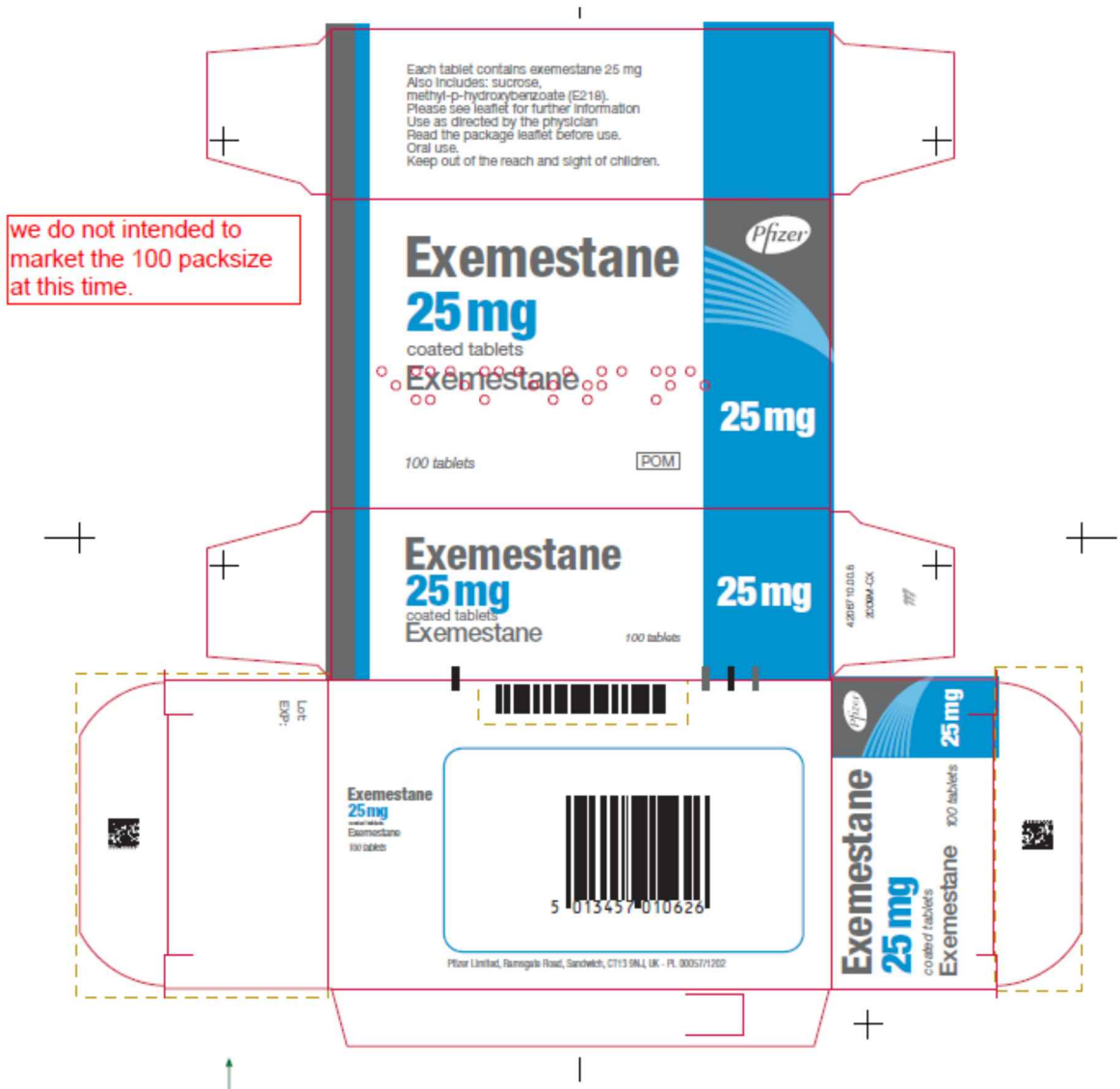
Lot: | Batch num. | Lotto
EXP: | Exp. Date | Scadenza


we do not intended to market the 100 packsize at this time.
Each tablet contains exemestane 25 mg
Also includes: sucrose, methyl-p-hydroxybenzoate (E218).
Please see leaflet for further information
Use as directed by the physician
Read the package leaflet before use.
Oral use.
Keep out of the reach and sight of children.
Exemestane
25 mg
coated tablets
Exemestane
100 tablets
POM
25 mg
Pfizer
Exemestane
25 mg
coated tablets
Exemestane
100 tablets
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Pfizer Limited, Ramsgate Road, Sandwich, CT13 9NJ, UK - PL 00057/1202
Exemestane
25 mg
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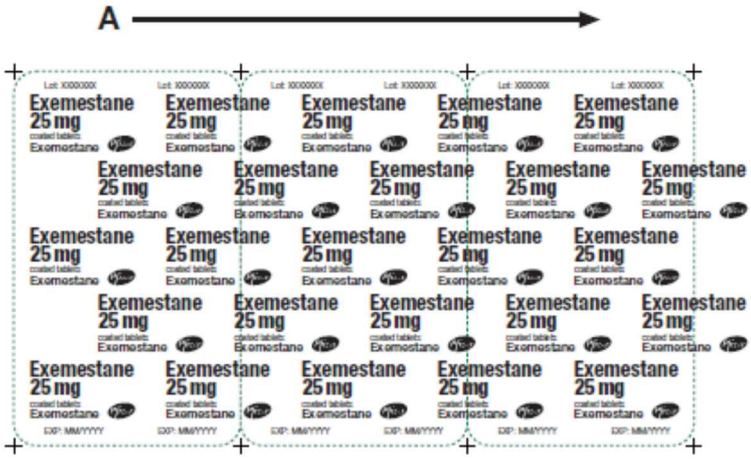
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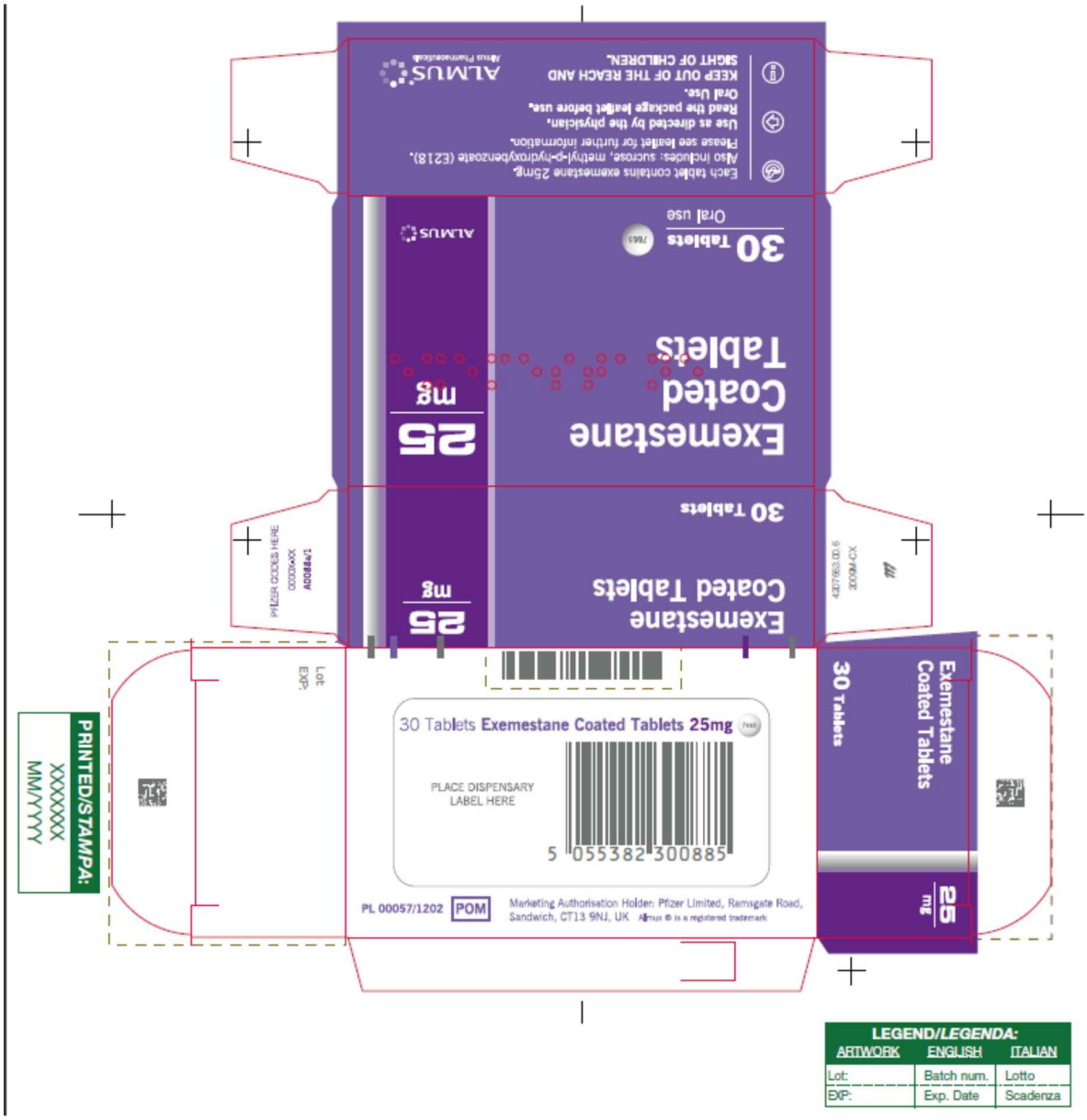
Exemestane
25 mg
Exemestane



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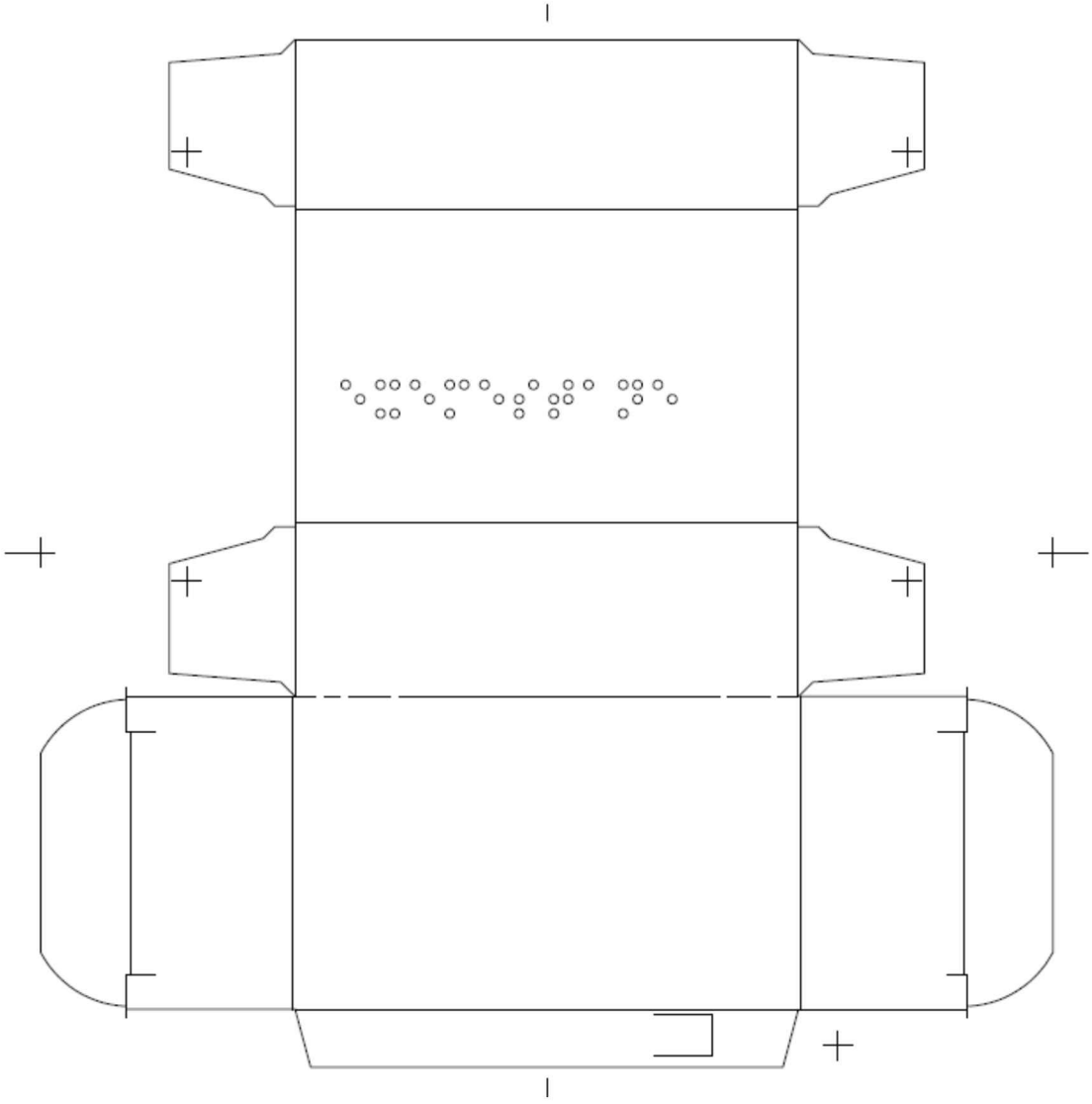
EXP:	Exp. Date	Scadenza



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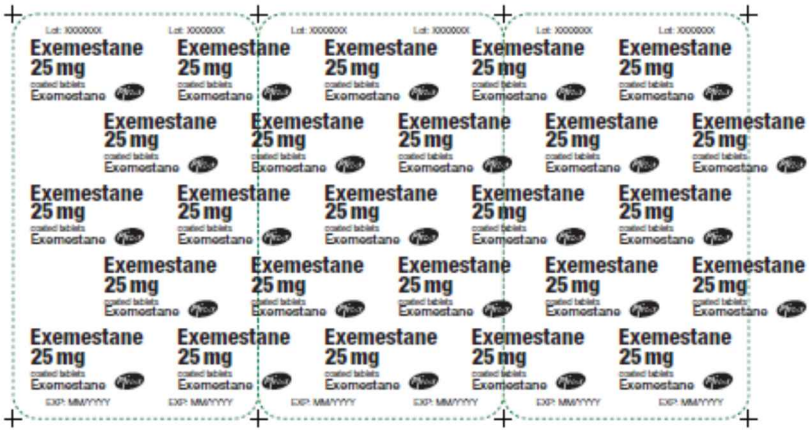
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Exemestane
25 mg
coated tablets
Exemestane
EXP: MM/YYYY


A
Lot: XXXXXXX
Exp: MM/YYYY
Exemestane
25 mg
coated tablets
Exemestane

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
To update section 5.1 (Pharmacodynamic properties) of the SPC with updated efficacy and safety data of exemestane for the adjuvant treatment of women with early breast cancer (EBC) obtained from the primary and secondary end point analysis of the 96-OEXE-031 main study at 87 months follow-up and the final analyses of the 96-OEXE-031 bone study. Intergroup Exemestane Study (IES) is added to the introductory text of section 4.8 (Undesirable effects) of the SPC.	UK/H/4519/001/II/002/G	SmPC sections 4.8 and 5.1	24/04/2012 24 May 2012	22/12/2012 22 December 2012	Approved on 03/01/2013	Yes-see Annex 1
To update sections 5.1 of the SmPC in line with the Marketing	UK/H/4519/001/II/007	SmPC section 5.1	22 May 2017	28 November 2017	Approved on 28 November 2017	Yes-see Annex 2

Authorisation Holder's (MAH) latest Core Data Sheet (CDS) Version 9.0 dated 24-Jan-2017. In addition minor editorial and formatting corrections were made in other sections of the SmPC. There are no consequential updates to the Patient Information Leaflet (PIL).						

ANNEX 1 – CLINICAL VARIATION ASSESSMENT REPORT

1 RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the variation application (UK/H/4519/001/II/002/G) for Exemestane, for updates to Sections 4.8 and 5.1 of the SmPC **is approvable**.

2 EXECUTIVE SUMMARY

2.1 SCOPE OF THE VARIATION

This variation concerns an update to the product information. The update is based on 87 months follow-up data from study 96-OEXE-031, a randomised double-blind trial in postmenopausal women with primary breast cancer who have received adjuvant tamoxifen for 2-3 years, comparing treatment until 5 years with adjuvant exemestane versus further tamoxifen. The final analysis of the 96-OEXE-031 bone sub study is also submitted.

One minor change is made to section 4.8, which is the addition of 'Intergroup Exemestane Study' (IES) in the introductory text. The rationale for the change is to provide the origin of the adverse event data. The vast majority of the changes are to section 5.1 of the SmPC and relate to the mature data derived from study 96-OEXE-031. There is a new section titled 'IES 87-Month Median Follow-up', which summarises the main efficacy data and the updated analysis from the bone sub study.

3 SCIENTIFIC DISCUSSION

Supportive Data
The Applicant has submitted full clinical study reports, a clinical overview, a summary of clinical efficacy, a summary of clinical safety and synopses of individual studies/substudy.

The clinical expert report is written by an appropriately qualified physician.

3.1 QUALITY ASPECTS

N/A

3.2 NON CLINICAL ASPECTS

N/A

3.3 CLINICAL ASPECTS

3.3.1 III.3.1 Clinical pharmacology

No new clinical pharmacology studies have been submitted by the Applicant.

3.3.2 III.3.2 Clinical efficacy

Study 96-OEXE-031
Briefly, Study 96-OEXE-031 was a randomised double-blind trial in postmenopausal women with primary breast cancer. The study was carried out between February 1998 and February 2003. After treatment for their primary disease, patients received tamoxifen continuously for between 24 and 37

months. Those who remained disease-free were considered eligible for entry into the study and were randomised to either exemestane (25 mg/day) or tamoxifen dosage (20 mg/day or 30 mg/day or if continuing, the same dose prior to randomisation). The primary efficacy end point was disease-free survival (DFS) and secondary endpoints included overall survival, breast cancer-free survival, contralateral breast cancer and distant recurrence-free survival.

Results
The majority of results were presented for the intention to treat (ITT) population and the Estrogen Receptor (ER) positive population. A total of 4740 female patients were randomised (366 study centres in 37 countries). There were 2352 patients in the exemestane group (86.2 % were ER positive) and 2372 patients in the tamoxifen group (85.3 % were ER positive). The median follow-up time from randomisation was 86.7 months (87.4 months for exemestane and 86.2 months for tamoxifen) and the median duration of study treatment was approximately 30 months (range: <0.1 to 40.4 months). Median post-treatment follow-up was approximately 5 years for both exemestane and tamoxifen arms.

Primary endpoint - Disease-Free Survival
After a median follow-up of 86.7 months, a total of 1193 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported. The most common first event was 'distant relapse'. The table below summarises the events in each arm and the unadjusted hazard ratio for DFS at 34.5 months, 52 months and 86.7 months median follow up duration.

Median follow up duration	**Exemestane arm (events)**	**Tamoxifen arm (events)**	**Unadjusted DFS hazard ratio (ITT)**
34.5 months	213	306	0.69 (95 % CI: 0.58, 0.82; p = 0.00003)
52 months	354	453	0.76 (95 % CI: 0.67, 0.88; p = 0.00015)
86.7 months	552	641	0.84 (95 % CI: 0.75, 0.94; p = 0.002)

Multivariate Analysis
Multivariate analysis by Cox regression was used to explore the influence of baseline prognostic factors on DFS (ER status, nodal status, previous chemotherapy, previous hormone replacement therapy (HRT) and use of bisphosphonates [Note - approximately 300 patients had missing data for at least 1 factor. These patients were excluded from the analysis]).

Of interest, ER status, nodal status and prior HRT influenced DFS:

- ER negative patients were 1.5 times more likely to relapse than ER positive patients
- Patients with >3 positive nodes were 3.5 times more likely to relapse than patients with negative nodal status
- Patients who had received prior HRT had a better outcome

Multivariate Analysis of Disease-Free Survival (ITT Population)

Factor	Comparison	Hazard Ratio	
		Hazard Ratio (95% CI)	p-value*
Treatment	Exemestane vs Tamoxifen	0.79 (0.70, 0.89)	<0.0001
ER status	Negative vs Positive	1.53 (1.11, 2.10)	0.0091
	Unknown vs Positive	1.16 (0.97, 1.39)	0.1118
Nodal status	≤3 Positive nodes vs Negative	1.70 (1.48, 1.96)	<0.0001
	>3 Positive nodes vs Negative	3.53 (3.00, 4.16)	<0.0001
Previous chemotherapy	Yes vs No	0.88 (0.77, 1.01)	0.0653
HRT	Yes vs No	0.68 (0.59, 0.80)	<0.0001
Bisphosphonates	Yes vs No	1.28 (0.82, 1.99)	0.2774

*Wald chi square test.
Source: 87-Month CSR, Table 13.04.09
ITT = Intent-to-treat; CI = Confidence interval; vs = Versus; ER = Estrogen receptor; HRT = Hormone replacement therapy

Assessor's comment
For the primary endpoint DFS, a smaller benefit was observed in the updated analysis when compared with previous analysis and the hazard ratio is closer to 1. The hazard ratio was 0.69 at 34.5 months, 0.76 at 52 months and 0.84 at 86.7 months. Although a smaller benefit was observed, the DFS benefit remains both statistically and clinically significant (16 % relative reduction in the risk of relapse with exemestane therapy).

Secondary endpoints
Secondary endpoints included overall survival, breast cancer free survival, distant recurrence free survival and contralateral breast cancer.

Statistical Analysis of Secondary End Points (ITT Population)

Secondary End Points	Kaplan Meier Probability at 3 Years After Randomization		Unadjusted Hazard Ratio (95% CIs)	p-value*
	Exemestane (N = 2352)	Tamoxifen (N = 2372)		
Time to Contralateral Breast Cancer	99.6%	99.0%	0.74 (0.50, 1.10)	0.12983
Overall Survival	95.3%	94.1%	0.89 (0.77, 1.02)	0.08972
Distant Recurrence Free Survival**	93.6%	91.1%	0.85 (0.74, 0.98)	0.02425
Breast Cancer Free Survival	92.5%	89.1%	0.82 (0.72, 0.94)	0.00263

Source: 87-Month CSR, Table 13.04.05 and Figures 14.2, 14.3, 14.4 and 14.5. *Log-rank test.
** Sponsor algorithm

Overall Survival (OS)
A trend for improved OS favouring exemestane was observed. The 87 month analysis was consistent with the prior analyses at 34.5 months and 52 months.

Median follow up duration	Exemestane arm (deaths)	Tamoxifen arm (deaths)	Unadjusted OS hazard ratio
34.5 months	-	-	0.86 (0.67, 1.10) 0.22962
52 months	-	-	0.85 (0.71, 1.02) 0.07362
86.7 months	373	420	0.89 (95% CI: 0.77, 1.02; p=0.08972)

Contralateral Breast Cancer
A trend in the reduction in the risk of developing invasive contralateral breast cancer was observed. Although exemestane reduced the risk of contralateral breast cancer, the result is no longer statistically significant.

Median follow up duration	Exemestane arm (events)	Tamoxifen arm (events)	Unadjusted hazard ratio
34.5 months	-	-	0.32 (0.15, 0.72) 0.00340
52 months	-	-	0.57 (0.33, 0.99) 0.04158
86.7 months	43	58	0.74 (95% CI: 0.50, 1.10; p=0.12983)

Breast Cancer-Free Survival
A statistically significant reduction in the risk of breast cancer relapse was observed.

Median follow up duration	Exemestane arm (events)	Tamoxifen arm (events)	Unadjusted hazard ratio
34.5 months	-	-	0.65 (0.54, 0.79) <0.00001
52 months	-	-	0.76 (0.65, 0.89) 0.00041
86.7 months	434	513	0.82 (95% CI: 0.72, 0.94; p=0.00263)

Distant Recurrence-Free Survival
A statistically significant reduction in the risk of developing distant metastases was observed.

Median follow up duration	Exemestane arm (events)	Tamoxifen arm (events)	Unadjusted hazard ratio
34.5 months	-	-	0.70 (0.56, 0.86) 0.00083
52 months	-	-	0.83 (0.70, 0.98) 0.02621
86.7 months	353	409	0.85 (95% CI: 0.74, 0.98; p=0.02425)

ER status subgroups
The large majority of patients were ER positive in both the exemestane (86.2 %) and tamoxifen (85.3 %) groups. The primary and secondary analysis for the ER positive population is displayed in the table below.

Summary of Primary and Secondary End Points in ER+ Population

End Point	Hazard Ratio (95% CIs)	p-value*
Disease Free Survival	0.83 (0.73,0.94)	0.00316
Overall Survival	0.87 (0.75, 1.02)	0.0831
Time to Contralateral Breast Cancer	0.70 (0.46, 1.05)	0.0836
Distant Recurrence Free Survival**	0.82 (0.70, 0.96)	0.01501
Breast Cancer Free Survival	0.81 (0.70, 0.93)	0.00303

Source: 87-Month CSR, Appendix A10.8. *Log-rank test **Sponsor algorithm

Assessor's comment
For the ITT population, significant improvements in DFS, breast cancer-free survival and distant recurrence-free survival were observed at a median follow-up of 87 months. The results for the primary and secondary endpoints for the ITT population were similar to the ER positive population.

3.3.3 III.3.3 Clinical safety

Main study 96-OEXE-031

All adverse events were collected from the time of first dose of study therapy until 30 days from discontinuation of study therapy. The majority of patients had completed or discontinued therapy at the cut-off date of February 2006. Fourteen patients were considered to be on treatment at the time of the 52 month analysis. The last patient treatment with study medication was on the 21st February 2006.

Summary

Treatment-emergent adverse events (AEs) and illnesses were reported by 1905/2249 patients (84.7 %) in the exemestane group and 1888/2279 patients (82.8 %) in the tamoxifen group. The most common AEs and illnesses were hot flushes, arthralgia and fatigue for exemestane and hot flushes, fatigue and headache for tamoxifen. There were no additional treatment-emergent SAEs or deaths reported in the 87 month clinical study report (CSR). The combined summary of treatment-emergent illnesses and AEs are presented in the 87 Month CSR, Table 13.06.13 (pages 470 - 585). A summary is provided below in the summary of clinical safety (SCS).

Treatment-Emergent Adverse Events and Illnesses Reported by ≥ 5% of Patients in Either Treatment Group or Between Treatment Comparisons Achieving Statistical Significance at 1% level in Study 96-OEXE-031 (As Treated - AE and Illness Safety Population)

MedDRA preferred term[a]	Exemestane (N = 2249)		Tamoxifen (N = 2279)		p-value*
	n	(%)	n	(%)	
Patients with any illness or AE	1905	(84.7%)	1888	(82.8%)	0.091
Hot flushes	491	(21.8%)	457	(20.1%)	0.144
Fatigue	367	(16.3%)	344	(15.1%)	0.270
Arthralgia	396	(17.6%)	246	(10.8%)	**<0.001**
Headache	304	(13.5%)	255	(11.2%)	0.019
Sweating increased	270	(12.0%)	242	(10.6%)	0.146
Insomnia	290	(12.9%)	206	(9.0%)	**<0.001**
Dizziness	224	(10.0%)	200	(8.8%)	0.185
Hypertension	223	(9.9%)	191	(8.4%)	0.080
Nausea	200	(8.9%)	208	(9.1%)	0.795
Back pain	208	(9.3%)	176	(7.7%)	0.070
Depression	140	(6.2%)	127	(5.6%)	0.377
Weight increased	128	(5.7%)	138	(6.1%)	0.614
Pain in limb	143	(6.4%)	108	(4.7%)	0.019
Osteoarthritis	138	(6.1%)	106	(4.7%)	0.030
Vaginal hemorrhage	89	(4.0%)	121	(5.3%)	0.034
Osteoporosis	116	(5.2%)	66	(2.9%)	**<0.001**
Diarrhea	95	(4.2%)	50	(2.2%)	**<0.001**
Hypercholesterolemia	82	(3.7%)	47	(2.1%)	**0.002**
Muscle cramp	32	(1.4%)	73	(3.2%)	**<0.001**
Parasthesia	62	(2.8%)	23	(1.0%)	**<0.001**
Carpal tunnel syndrome	63	(2.8%)	5	(0.2%)	**<0.001**
Thromboembolism	16	(0.7%)	42	(1.8%)	**<0.001**
Uterine polyp	8	(0.4%)	41	(1.8%)	**<0.001**
Uterine polypectomy	4	(0.2%)	19	(0.8%)	**0.003**
Endometrial hyperplasia	1	(<0.1%)	20	(0.9%)	**<0.001**
Gastric ulcer	16	(0.7%)	1	(<0.1%)	**<0.001**
Neuropathy	12	(0.5%)	2	(0.1%)	**0.007**

*Fisher's Exact test (two-tailed). p-values achieving significance in bold.
Source: 87-Month CSR, Table 13.06.14
AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; N = Total number of subjects; n = Number of subjects with specified AE or illness
[a] Events were monitored using 2 separate positive checklists; 1 for illnesses and 1 for AEs.

Endometrial substudy
The endometrial substudy was completed and reported in the 52 month submission (see UK/H/326/001/II/029).

Bone substudy 96-OEXE-031
The bone study was conducted at 17 centres in 8 countries. The aim of the study was to investigate the effects of exemestane and tamoxifen on bone mineral density (BMD) and bone metabolism. The primary objective was to compare changes in BMD between the two groups after 12 months and 24 months of randomised treatment. The change in BMD compared with baseline was measured at four sites: the lumbar spine, femoral neck, total hip and Ward's triangle.

The initial observations from the bone substudy were added to the SmPC at the time of the 52 month analysis (UK/H/326/001/II/029). The supplemental CSR contains additional data for up to 36 months on treatment and up to 24 months after treatment discontinuation with a last visit date of 26 February 2008 and a database lock date of 23 April 2009.

At the 36-month on treatment assessment, the mean percent change in lumbar spine density was:
- -3.37 % on exemestane
- -1.29 % on tamoxifen

At the 24-month post treatment assessment, the mean percent change in lumbar spine density was:
- -2.17 % on exemestane
- -3.44 % on tamoxifen

At the 36-month assessment on treatment assessment, the mean percent change in total hip density was:

- -2.96 % on exemestane
- -2.02 % on tamoxifen

At the 24-month post treatment assessment, the mean percent change in total hip density was:

- -3.06 % on exemestane
- -4.15 % on tamoxifen

Bone Mineral Density over Time: Mean Absolute value (g/cm^2) and Mean Percent Change from Baseline for the Exemestane Treatment Group (Evaluable Population)

		On-treatment				Post-treatment		
	Baseline	**6 mth**	**12 mth**	**24 mth**	**36 mth**	**1-6 mth**	**12 mth**	**24 mth**
Spine	**N=86**	**N=84**	**N=82**	**N=82**	**N=32**	**N=11**	**N=71**	**N=74**
Mean	1.05	1.03	1.03	1.01	1.02	1.04	1.03	1.04
(SD)	(0.15)	(0.16)	(0.16)	(0.16)	(0.13)	(0.19)	(0.15)	(0.15)
Mean percent change from baseline	N/A	-2.64	-2.98	-3.69	-3.37	-4.39	-3.14	-2.17
Total hip	**N=86**	**N=82**	**N=82**	**N=79**	**N=34**	**N=12**	**N=71**	**N=73**
Mean	0.96	0.95	0.93	0.94	0.93	0.88	0.93	0.94
(SD)	(0.12)	(0.12)	(0.11)	(0.12)	(0.09)	(0.11)	(0.11)	(0.11)
Mean percent change from baseline	N/A	-1.31	-2.17	-2.81	-2.96	-3.15	-3.06	-3.06
Femoral neck	**N=86**	**N=82**	**N=82**	**N=78**	**N=31**	**N=12**	**N=62**	**N=61**
Mean	0.88	0.86	0.86	0.85	0.84	0.79	0.83	0.84
(SD)	(0.13)	(0.13)	(0.13)	(0.13)	(0.10)	(0.13)	(0.11)	(0.12)
Mean percent change from baseline	N/A	-1.91	-2.56	-4.00	-4.16	-6.16	-4.92	-4.10
Ward's triangle	**N=85**	**N=82**	**N=81**	**N=72**	**N=31**	**N=12**	**N=58**	**N=60**
Mean	0.72	0.70	0.69	0.68	0.68	0.65	0.67	0.67
(SD)	(0.15)	(0.15)	(0.15)	(0.14)	(0.13)	(0.13)	(0.13)	(0.13)
Mean percent change from baseline	N/A	-2.02	-3.51	-4.75	-4.74	-6.64	-6.88	-6.07

Source: Bone Substudy CSR Tables 13.11.01.01, 13.11.02.01, 13.11.03.01, 13.11.04.01.
Note: Patients were evaluable if they were treated for at least 9 months and had baseline and Month 12 and/or Month 24 assessments.
Mth = month; SD = standard deviation.

Bone Mineral Density over Time: Mean Absolute Value (g/cm2) and Mean Percent Change from Baseline for the Tamoxifen Treatment Group (Evaluable Population)

		On-treatment				Post-treatment		
	Baseline	**6 mth**	**12 mth**	**24 mth**	**36 mth**	**1-6 mth**	**12 mth**	**24 mth**
Spine	**N=99**	**N=96**	**N=96**	**N=92**	**N=46**	**N=12**	**N=83**	**N=81**
Mean	1.08	1.08	1.07	1.06	1.07	1.13	1.05	1.04
(SD)	(0.15)	(0.16)	(0.15)	(0.15)	(0.15)	(0.13)	(0.14)	(0.14)
Mean percent change from baseline	-	-0.22	-0.19	-0.47	-1.29	-1.03	-3.12	-3.44
Total hip	**N=99**	**N=96**	**N=95**	**N=93**	**N=44**	**N=13**	**N=85**	**N=84**
Mean	0.98	0.98	0.97	0.96	0.96	1.01	0.94	0.94
(SD)	(0.13)	(0.12)	(0.12)	(0.12)	(0.13)	(0.13)	(0.12)	(0.12)
Mean percent change from baseline	-	-0.13	-0.39	-0.91	-2.02	-1.65	-3.46	-4.15
Femoral neck	**N=97**	**N=94**	**N=95**	**N=89**	**N=40**	**N=11**	**N=78**	**N=69**
Mean	0.90	0.90	0.90	0.89	0.87	0.93	0.86	0.85
(SD)	(0.14)	(0.14)	(0.14)	(0.14)	(0.14)	(0.11)	(0.14)	(0.14)
Mean percent change from baseline	-	-0.30	-0.32	-0.78	-3.15	-1.81	-3.85	-4.95
Ward's triangle	**N=97**	**N=94**	**N=95**	**N=87**	**N=40**	**N=11**	**N=76**	**N=68**
Mean	0.74	0.75	0.72	0.72	0.70	0.75	0.69	0.68
(SD)	(0.17)	(0.17)	(0.16)	(0.16)	(0.17)	(0.11)	(0.15)	(0.16)
Mean percent change from baseline	-	0.32	-1.30	-1.86	-4.46	-5.44	-6.45	-8.60

Source: Bone Substudy CSR Tables 13.11.01.01, 13.11.02.01, 13.11.03.01, 13.11.04.01
Note: Patients were evaluable if they were treated for at least 9 months and had baseline and Month 12 and/or Month 24 assessments.
Mth = month; SD = standard deviation.

Fractures

Seventeen patients in the bone substudy were reported as having fractures during the study:

- 7 of 101 (6.9 %) on exemestane
- 10 of 105 (9.5 %) on tamoxifen

For the main study (including the follow-up period), the all fracture rate was significantly higher in the exemestane group:

- 7.3 % on exemestane
- 5.2 % on tamoxifen

Assessor's comment
There were no additional treatment-emergent SAEs or deaths in the reporting period. Bone mineral density was shown to decrease over time in both treatment groups. However, the bone loss was more marked during the period of active treatment for exemestane. At 24 months post-treatment, the overall reductions in BMD were higher in the tamoxifen arm. The fracture rate was higher in the exemestane treated group. Overall, there are no significant changes in the safety profile and the risk benefit assessment remains favourable.

3.4 PRODUCT INFORMATION

3.4.1 III.4.1 Summary of Product Characteristics

The proposed changes are considered to be acceptable.

3.4.2 III.4.2 Package leaflet and user test

No changes have been made to the package leaflet.

3.4.3 III.4.3 Labelling

No changes have been made to the label.

4 OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Study 96-OEXE-031 is a pivotal adjuvant therapy trial in postmenopausal women who remained disease-free after 2 to 3 years of tamoxifen therapy. The updated efficacy results confirm previously observed analyses for both the primary and secondary endpoints. Overall, there are no significant changes to the safety profile of exemestane and no new safety concerns have emerged. The benefit risk assessment remains positive for the sequential adjuvant therapy with exemestane after 2 to 3 years of tamoxifen therapy.

5 REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

None

Annex 2

VARIATION ASSESSMENT REPORT

Our Reference:	PL 00057/1202 - 0015
Product:	PL 00057/0930 AROMASIN TABLETS 25MG
Marketing Authorisation Holder:	PFIZER LIMITED
Active Ingredient(s):	EXEMESTANE.
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	UK/H/4519/001/II/007

Reason:

To update section 5.1 of the SmPC in line with the Marketing Authorisation Holder's (MAH) latest Core Data Sheet (CDS) Version 9.0 dated 24-Jan-2017. In addition minor editorial and formatting corrections were made in other sections of the SmPC. There are no consequential updates to the Patient Information Leaflet (PIL).

Linked / Related Variation(s) or Case(s):

The Assessment Report refers to the following submission PL 00057/1202 – 0015 (UK/H/4519/001/II/007).

This is a worksharing procedure, which has procedure number: UK/H/xxxx/WS/270.

The Concerned Member States are: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

Supporting Evidence

The clinical overview summarised the efficacy and safety of the IES trial after a median duration of therapy of about 30 months and a median follow-up of about 119 months (final follow-up), with minmal details.

Detailed description of the results was mentioned to be available in the CSR which has been provided by the Applicant.

Evaluation

The addition of the following paragraph is proposed in Section 5.1 of the SmPC.
The applicant has also submitted a table summarising the objective outcomes which has been proposed for inclusion in the SmPC under IES 119-month final follow-up within section 5.1:

IES 119-month final follow-up
After a median duration of therapy of about 30 months and a median follow-up of about 119 months, results showed that sequential treatment with exemestane after 2 to 3 years of adjuvant tamoxifen therapy was associated with a clinically and statistically significant improvement in DFS compared with continuation of tamoxifen therapy. Analysis showed that over the observed study period exemestane reduced the risk of breast cancer recurrence by 14% compared with tamoxifen (hazard ratio 0.86, p = 0.00393). The beneficial effect of exemestane over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Exemestane also significantly prolonged breast cancer-free survival (hazard ratio 0.83, p<0.00152), and distant recurrence-free survival (hazard ratio 0.86, p = 0.02213). Exemestane also reduced risk of contralateral breast cancer; however, the effect was no longer statistically significant (hazard ratio 0.75, p = 0.10707).

In the whole study population, overall survival was not statistically different between the two groups with 467 deaths (19.9%) occurring in the exemestane group and 510 deaths (21.5%) in the tamoxifen group (hazard ratio 0.91, p = 0.15737, not adjusted for multiple testing). For the subset of patients with oestrogen receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.89 (log-rank test: p = 0.07881) in the exemestane group relative to the tamoxifen group.

In the whole study population, a statistically significant 14% reduction in the risk of dying (hazard ratio for OS 0.86; Wald chi square test: p = 0.0257) was observed for exemestane compared with tamoxifen when adjusting for the pre-specified prognostic factors (i.e., ER status, nodal status, prior chemotherapy, use of HRT and use of bisphosphonates).

A lower incidence of other second (non-breast) primary cancers was observed in exemestane-treated patients compared with tamoxifen only-treated patients (9.9% versus. 12.4%).

In the main study, which had a median follow-up in all participants of 119 months (0 – 163.94) and median duration of exemestane treatment of 30 months (0 – 40.41), the incidence of bone fractures was reported on 169 (7.3%) patients in the exemestane group compared with 122 (5.2%) patients in the tamoxifen group (p=0.004).

Efficacy Results From IES in Postmenopausal Women With Early Breast Cancer (ITT)

	No. of Events		Hazard Ratio	
	Exemestane	Tamoxifen	Hazard Ratio	p-value
30-Month Median Treatment and 34.5-Month Median Follow-Up				
Disease-free survival[a]	213	306	0.69 (95% CI: 0.58-0.82)	0.00003
Breast cancer-free survival[b]	171	262	0.65 (95% CI: 0.54-0.79)	<0.00001
Contralateral breast cancer	8	25	0.32 (95% CI: 0.15-0.72)	0.00340
Distant recurrence-free survival[c]	142	204	0.70 (95% CI: 0.56-0.86)	0.00083
Overall survival[d]	116	137	0.86 (95% CI: 0.67-1.10)	0.22962
30-Month Median Treatment and 52-Month Median Follow-Up				
Disease-free survival[a]	354	453	0.77 (95% CI: 0.67-0.88)	0.00015
Breast cancer-free survival[b]	289	373	0.76 (95% CI: 0.65-0.89)	0.00041
Contralateral breast cancer	20	35	0.57 (95% CI: 0.33-0.99)	0.04158
Distant recurrence-free survival[c]	248	297	0.83 (95% CI: 0.70-0.98)	0.02621
Overall survival[d]	222	262	0.85 (95% CI: 0.71-1.02)	0.07362
30-Month Median Treatment and 87-Month Median Follow-Up				
Disease-free survival[a]	552	641	0.84 (95% CI: 0.75-0.94)	0.002
Breast cancer-free survival[b]	434	513	0.82 (95% CI: 0.72-0.94)	0.00263
Contralateral breast cancer	43	58	0.74 (95% CI: 0.50-1.10)	0.12983
Distant recurrence-free survival[c]	353	409	0.85 ((95% CI: 0.74-0.98)	0.02425
Overall survival[d]	373	420	0.89 (95% CI: 0.77-1.02)	0.08972
30-Month Median Treatment and 119-Month Median Follow-Up				
Disease-free survival[a]	672	761	0.86 (95% CI: 0.77-0.95)	0.00393
Breast cancer-free survival[b]	517	608	0.83 (95% CI: 0.74-0.93)	0.00152

Efficacy Results From IES in Postmenopausal Women With Early Breast Cancer (ITT)

	No. of Events		Hazard Ratio	
	Exemestane	Tamoxifen	Hazard Ratio	p-value
Contralateral breast cancer	57	75	0.75 (95% CI: 0.53-1.06)	0.10707
Distant recurrence-free survival[c]	411	472	0.86 (95% CI: 0.75-0.98)	0.02213
Overall survival[d]	467	510	0.91 (95% CI: 0.81-1.04)	0.15737

CI = confidence interval; IES = Intergroup Exemestane Study; ITT = intention-to-treat.

a. Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer or death from any cause.

b. Breast cancer-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer or breast cancer death.

c. Distant recurrence-free survival is defined as the first occurrence of distant recurrence or breast cancer death.

d. Overall survival is defined as occurrence of death from any cause.

Section 5.1 of the SmPC reflects the summary given in the clinical overview. The Applicant has provided the final clinical study report (CSR), from which the data were derived, and has also included relevant supporting evidence in the clinical overview. The Applicant also provided a Summary of Changes to the CSR. The latter added the name of a new statistical lead, and corrected an error in a statement about the overall survival for a subset of patients with oestrogen receptor-positive or unknown status in the CSR (changed from statistically significant to not statistically significant [p=0.07881]). With regards to fracture risks, the Applicant explained that the Intergroup Exemestane Study (IES) design did not include a 119-month post-treatment follow-up period for either the Bone Substudy or the Endometrial Substudy. In addition, the design of the Endometrial Substudy did not include a fracture endpoint. However, in the main study, which had a median follow-up in all participants of 119 months (0-163.94) and median duration exemestane treatment of 30 months (0-40.41), 169 (7.3%) patients in the exemestane group had fractures compared with 122 (5.2%) patients in the tamoxifen group, p = 0.004. These figures are the same as under IES 87-month median follow-up. The Applicant proposes to add a statement about this under IES 119-month final follow-up section.

Summary of the safety data was brief in the clinical overview.

Assessment of applicant's response

The proposed addition of the above paragraph and table (in italics) to Section 5.1 of the SmPC is acceptable.

Decision – Approve