

Public Assessment Report

Scientific discussion

Exemestan “Sandoz” 25 mg film-coated tablets

Exemestane

DK/H/1732/001/DC

This module reflects the scientific discussion for the approval of Exemestan “Sandoz”. The procedure was finalised on 22 April 2010. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Exemestan “Sandoz” 25 mg film-coated tablets, from Sandoz A/S. The product was authorised in Denmark on 17 May 2010. The product is indicated for:

- the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy.
- the 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.

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. 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.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Aromasin coated tablets by Pfizer, registered since 14 October 1999 in Denmark.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC (generic application) and article 10.2(b) of Directive 2004/27/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 25 mg of exemestane.

The tablets are white to off-white, round, biconvex film-coated tablets debossed with ‘E25’ on one side and plain on the other.

The tablets are packed in white opaque PVC/PVdC-Alu blisters in pack sizes of 15, 20, 28, 30, 90, 98, 100 and 120 tablets. However, not all pack sizes may be marketed.

The excipients in the tablet core are: Mannitol; cellulose microcrystalline; crospovidone; sodium starch glycolate (type A); hypromellose E5; polysorbate 80; colloidal anhydrous silica and magnesium stearate.

The tablet coating consists of: Hypromellose 6cp (E464); macrogol (400) and titanium dioxide (E171).

Compliance with Good Manufacturing Practice

The RMS 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.

II.2 Drug Substance

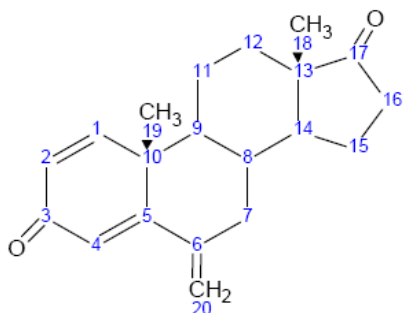
INN: Exemestane

Chemical name(s): 6-methylene-androsta-1,4-diene-3,17-dione

Molecular formula: C₂₀H₂₄O₂

Molecular mass: 296.4

Molecular structure:



Exemestane is a white to ivory-white crystalline powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in alcohol.

The documentation on the active substance exemestane is presented as a European Drug Master File/Active Substance Master File (DMF).

The drug substance specification is compliant with general ICH requirements for specifications and includes limits on particle size distribution.

Based on the presented stability data an appropriate retest period has been set.

II.3 Medicinal Product

The composition of the product is adequately described. The choice of excipients is justified and their functions explained satisfactory. The container is well known and applicability demonstrated in stability studies.

The manufacturing is a standard wet granulation. Satisfactory validation of the manufacturing process is provided.

The product specification covers appropriate parameters for this dosage form and includes relevant physicochemical, identification, assay and purity tests. Validations of the analytical methods have been presented. Batch analysis has been performed on two production scale batches of the formulation and complies in general with the release requirements and confirms the consistency of the product manufacture.

The conditions used in the stability studies are according to the ICH stability guideline. Stability data are provided for the proposed strength in the packaging materials intended for marketing. Results at long term storage are available for 18 months do not show significant changes and extrapolation of shelf-life to 30 months storage time is accepted without further storage conditions.

III. NON-CLINICAL ASPECTS

This product is a generic formulation of Aromasin coated tablets, which are 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Exemestane is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted 3 bioequivalence studies (two studies under fasting conditions and one study under fed conditions) in which the pharmacokinetic profile of the test product Exemestan “Sandoz” 25 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Aromasin coated tablets by Pfizer.

1 - Single-dose study under fasting conditions

The study was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study of exemestane 25 mg film-coated tablets in comparison with Aromasin 25 mg coated tablets in healthy, postmenopausal human female subjects conducted under fasting conditions with a wash out period of 10 days between the administration of one 25 mg exemestane tablet in each period.

Blood samples were collected at pre-dosing and at 0.167, 0.333, 0.50, 0.667, 0.833, 1.00, 1.167, 2.000, 2.333, 2.667, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 18.00, 24.00, 36.00, 48.00, 72.00, 96.00 and 120.00 hrs post administration of a single-dose 25 mg tablet with 240 ml of water for the analyses of exemestane in plasma.

64 healthy post menopausal female subjects (51.0 ± 3.89 years) participated in the study. 62 subjects completed the study. One subject was withdrawn due to emesis and another subject on medical grounds.

The parameters calculated were AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , λ_z and $t_{1/2el}$. Primary variables were AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Bioequivalence was concluded if C_{max} and AUC_{0-t} are within 80.00%-125.00%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	62.913 \pm 21.7158	71.493 \pm 22.3634*	24.827 \pm 12.3241	0.667	25.266 \pm 12.1648*
Reference	61.360 \pm 20.6766	71.838 \pm 23.8792*	21.558 \pm 11.7788	0.833	25.035 \pm 15.1004*
#Ratio (90% CI)	97.91-106.83%	91.79-100.64%*	106.00- 129.70%	-	-
CV (%)	14.6%	12.2%	34.6%		

AUC_{0-∞}	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

*Calculation based on n=49 for reference and n=44.

The test product did not meet the bioequivalence criteria with respect to extent of absorption as C_{max} ratio (90% CI) was 106.00-129.70% i.e. above upper limit of 125.00% which may be explained by the high intra-subject variability of 34.6%.

2 - Single-dose study under fasting conditions

The study was an open-label, randomized, balanced, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions in normal, adult, healthy, male and post menopausal female subjects with a wash out period of at least 10 days between the two administrations. 25 mg exemestane was administered in each period.

Blood samples were collected in Na-heparin vacutainers at pre-dosing and at 00.167, 00.333, 00.500, 00.667, 00.833, 01.000, 01.167, 01.333, 01.500, 1.667, 01.833, 02.000, 02.167, 02.333, 02.500, 02.667, 02.833, 03.000, 03.333, 03.667, 04.000, 04.500, 05.000, 06.000, 08.000, 12.000, 16.000, 20.000, 24.000, 36.000, 48.000, 72.000, 96.000 and 120.000 hrs post administration of a single-dose exemestane 25 mg tablet with 240 ml of water for the analyses of exemestane in plasma.

80 healthy subjects – 50 males and 30 females in the age group of 19 to 64 years participated in the study. 79 subjects completed the study and were included in the analysis.

One subject was withdrawn due to adverse event during the first treatment period.

The parameters calculated were AUC_{0-t}, AUC_{0-∞}, C_{max}, t_{max}, K_{el} and t_{1/2 el}. Primary variables were AUC_{0-t}, AUC_{0-∞} and C_{max}.

Bioequivalence was concluded if the ratio and the 90% confidence interval for both falls within the acceptable range of 80.00 %-125.00 % for log transformed C_{max}, AUC_{0-t} and AUC_{0-inf}.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h	T _{1/2} h	K _{el} h
Test	57.78 ± 21.90	64.77 ± 25.66	27.84 ± 13.40	0.84 ± 0.42	18.05 ± 21.30	0.09 ± 0.17
CV (%)	37.91	39.61	48.12	49.98	-	-
Reference	62.00 ± 22.44	70.16 ± 26.72	25.42 ± 10.46	1.02 ± 0.68	20.43 ± 18.08	0.07 ± 0.06
CV (%)	36.19	38.09	41.14	66.29	-	-
*Ratio (90% CI)	89.36 80.60-99.07	88.87 80.13-98.56	105.19 94-93- 116.56	-	-	-
Intra subject variability (%)	40.47	40.25	40.25	-		
Inter subject variability (%)	32.65	33.60	36.70	-	-	-

AUC_{0-∞}	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
K_{el}	Elimination rate constant

*log-transformed values

The data demonstrates bioequivalence between the test and reference products, as the 90% CI are within 80.00 %-125.00 % for log transformed C_{max} , AUC_{0-t} and AUC_{0-inf} .

Single-dose study under fed conditions

The study was an open-label, randomized, balanced, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fed conditions in normal, adult, healthy post menopausal female subjects with a wash out period of at least 10 days between the two administrations. 25 mg exemestane was administered in each period.

Blood samples were collected pre-dosing and at 0.500, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.667, 4.00, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, 12.0, 18.0, 24.0, 30.00, 36.00, 48.00, 72.00, 96.00 and 120.00 hours post administration of a single-dose dose exemestane 25 mg tablet with 240 ml of water for the analyses of exemestane in plasma.

80 healthy Asian female subjects (52.2 ± 5.55 years) participated in the study. 79 subjects completed the study. One subject in group I discontinued due to protocol deviation.

The pharmacokinetic parameters calculated were AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , t_{max} , K_{el} and $t_{1/2}$ el. Primary variables: AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} .

Bioequivalence was concluded if the ratio and the 90% confidence interval for both falls within the acceptable range of 80.00 %-125.00 % for log transformed C_{max} , AUC_{0-t} and AUC_{0-inf} .

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range)

Table-C: Descriptive Statistics of Formulation Means for Exemestane (n=79)

Parameters (Units)	Mean \pm SD (Un-transformed data)	
	Reference Product-A	Test Product-B
T_{max} (h)*	2.000	2.000
C_{max} (ng / mL)	27.128 \pm 15.6531	25.198 \pm 14.4676
AUC_{0-t} (ng.h / mL)	72.903 \pm 27.4729	72.868 \pm 29.3644
$AUC_{0-\infty}$ (ng.h / mL)	78.924 \pm 29.5132 [#]	78.209 \pm 31.8470 [^]
λ_z (1 / h)	0.072 \pm 0.0493 [#]	0.076 \pm 0.0593 [^]
$t_{1/2}$ (h)	15.770 \pm 12.6360 [#]	13.491 \pm 9.0167 [^]
$AUC_{\%}$ Extrapolation Obs (%)	7.076 \pm 4.2776 [#]	6.657 \pm 3.3136 [^]

* T_{max} is represented as median value. #:n=73 and ^:n=70

Note: $AUC_{\%}$ Extrapolation obs (%) was $>20\%$ for six subjects in reference and nine subjects in test. Hence, the number of subjects used for computation of $AUC_{0-\infty}$, λ_z , $t_{1/2}$, $AUC_{\%}$ Extrapolation obs (%) was 73 for reference and 70 for test product.

Table-D: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Exemestane (n=79)

Parameters (Units)	ln-transformed data			
	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Test Product-B	Reference Product-A	Ratio (B / A)%	
C _{max} (ng / mL)	22.007	23.488	93.7	86.00-102.08%
AUC _{0-t} (ng.h / mL)	67.454	68.280	98.8	95.00-102.73%
AUC _{0-∞} (ng.h / mL)	72.334 [^]	73.847 [#]	98.0	94.25-101.79%

#: n=73 and ^: n=70

Intra-subject CV%: C_{max}: 33.2%; AUC_{0-t}: 14.8%; AUC_{0-∞}: 13.6%.

The data demonstrates bioequivalence between the test and reference products, as the 90% CI are within 80.00 %-125.00 % for log transformed C_{max}, AUC_{0-t} and AUC_{0-inf} under fed conditions.

Based on the studies submitted, it can be concluded that bioequivalence between the reference product and the product proposed for marketing has been demonstrated.

The RMS 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).

IV.2 Risk management plan & Pharmacovigilance system

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.

The Pharmacovigilance system described 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 identification and notification of any potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Aromasin coated tablets marketed by Pfizer.

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 language used for the purpose of user testing the package leaflet was English. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Exemestan “Sandoz” 25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Aromasin coated tablets by Pfizer. 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 has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other exemestane containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Exemestan “Sandoz” with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 22 April 2010. Exemestan “Sandoz” was authorised in Denmark on 17 May 2010.

A European harmonised birth date (1998-12-16) has been allocated. The next data lock point for exemestane is November 2010, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 22 April 2015.

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

Drug substance, DMF:

1. The complete validation of the analytical method for determination of p-toluenesulfonic acid ethyl ester will be performed in accordance with ICH Q2 (R1) not later than Q4 2010.

Drug product:

2. The applicant commits to perform process validation on three consecutive batches with a batch size of 300,000 tablets and a third batch of 100,000 tablets.
3. The drug product manufacturer commits to perform hold time study on one commercial batch of exemestane 25 mg tablets to confirm 1 month holding time on blend, core tablets and coated tablets.