CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Anastrozol Mylan 1 mg film-coated tablets
Mylan B.V., the Netherlands

anastrozole

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow–organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/838/01/DC
Registration number in the Netherlands: RVG 34008

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Pharmacotherapeutic group:	hormone antagonists and related agents, enzyme inhibitors
ATC code:	L02BG03
Route of administration:	oral
Therapeutic indication:	treatment of advanced breast cancer in postmenopausal women, adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer, and adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.
Prescription status:	prescription only
Date of authorisation in NL:	3 October 2007
Concerned Member States:	AT, BE, CZ, DE, DK, ES, FI, FR, GR, HU, IE, IT, NO, PL, PT, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Anastrozol Mylan 1 mg, film-coated tablets, from Mylan B.V., the Netherlands. The product is indicated for the treatment of advanced breast cancer in postmenopausal women, adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer, and adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SPC).

Anastrozole is a potent, orally active, non-steroidal aromatase inhibitor that markedly reduces the levels of circulating estrogens in postmenopausal women with breast cancer. It has been shown to offer significant clinical benefits in the treatment of post-menopausal women with early as well as advanced breast cancer. The recommended dosage is one tablet (1 mg) once a day.

It concerns a generic application claiming essential similarity with the innovator product Arimidex® film-coated tablets 1 mg, containing 1 mg of anastrozole, which has been registered in the United Kingdom by AstraZeneca UK Limited since August 1995. In addition, reference is made to Arimidex authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Arimidex film-coated tablets 1 mg, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture has no influence on efficacy and safety. A 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.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is anastrozole, an established active substance. The active substance is not described in a pharmacopoeia. The tests, which were performed on anastrozole, reflect the tests normally described in pharmacopoeial monographs with a general accepted limits. The limits for the impurities are based on the ICH guideline Q3A: “Impurities testing guideline: Impurities in new drug substances”. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

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.

Quality control of drug substance
The tests, which were performed on anastrozole, reflect the tests normally described in pharmacopoeial monographs with a general accepted limits. The limits for the impurities are based on the ICH guideline Q3A: “Impurities testing guideline: Impurities in new drug substances”. The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance(s) have been provided for 3 commercial scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. The drug substance is also photostable.

Medicinal Product

Composition
The white film-coated round biconvex tablets are debossed with “ANA” and “1” on one side.

The tablets contain 1 mg of the drug substance (anastrozole). The excipients are:
Core: lactose monohydrate, sodium starch glycolate type A, povidone K31 (E1201), magnesium stearate (E572).
Coating: macrogol 400, hypromellose (E464), titanium dioxide (E171).

The excipients, and the quantities of the excipients used, are all common in immediate release tablets.

Anastrozol Mylan 1 mg, film-coated tablets are packed in PVC/PE/PVDC-Aluminium blisters.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The goal was to develop a film-coated tablet that was essentially similar to the innovators product Arimidex 1mg. The *in vitro* dissolution profile and the uniformity of the content were targets for development to achieve essential similarity. No differences in the uniformity of the content and the dissolution characteristics were observed.

Excipients
All ingredients used, are well known and widely used as pharmaceutical excipients and comply with the relevant Ph.Eur.* specifications.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 commercial size batches in accordance with the relevant European guidelines. The composition of the tablets and manufacturing process used to manufacture the three validation batches is identical to the manufacturing process as described for the commercial batches.
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph. Eur. and includes tests for appearance, identification, uniformity of dosage unit, water content, dissolution, impurities, assay of the active substance and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided from 3 batches in accordance with applicable European guidelines demonstrating the stability of the product for 30 months, when stored in the original package. No specific additional storage conditions are necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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

II.2 Non-clinical aspects

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

Environmental risk
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of anastrozole released into the environment. It does not contain any component which result in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Anastrozol Mylan, 1 mg tablet (Mylan B.V., the Netherlands) is compared with the reference product Arimidex 1 mg tablet (AstraZeneca, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product in different EU member states.

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

Anastrozole may be taken once daily without reference to food intake. Therefore, the bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 NfG on the investigation of bioavailability and bioequivalence.

Bioequivalence study
A randomized, open-label, single dose, 2-way cross-over, laboratory-blind comparative bioavailability study was carried out under fasting conditions in post-menopausal female subjects.
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

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

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	576 ± 202	628 ± 214	15.5 ± 2.3	1.38 (1-2.5)	41 ± 15
Reference	581 ± 193	629 ± 207	15.6 ± 2.5	1.25 (1-2.5)	40 ± 12
***Ratio (90% CI)**	0.99 (0.95-1.02)	1.00 (0.97-1.03)	1.00 (0.96-1.04)	---	---
CV (%)	7	6	9	---	---

$AUC_{0-\infty}$ 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} were found within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters, it can be concluded that test Anastrozol Mylan 1 mg tablet and reference Arimidex 1 mg tablet (AstraZeneca, Germany) are bioequivalent with respect to rate and extent of absorption of anastrozole, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Anastrozole was first approved in 1995 in the United Kingdom, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of anastrozole can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant 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 Risk Management Plan is not necessary for this product. Therefore, the submission of PSUR 3 years after the marketing of the product is supported.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Arimidex 1 mg tablet marketed by AstraZeneca BV.

Readability test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Anastrozol Mylan, 1 mg film-coated tablets, have a proven chemical-pharmaceutical quality and are generic forms of Arimidex. Arimidex is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is consistent with that of the reference product. The SPC, Package Leaflet (PL) and Labelling are in the agreed templates. Braille conditions are met by the MAH.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The Board followed the advice of the assessors. The Member States, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Anastrozol Mylan, 1 mg with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure.

The PSUR submission cycle is 3 years.

The date for the first renewal will be 10 May 2012.

The following post-approval commitments were made during the procedure:

Quality

- Stability testing of the drug substance should continue throughout the proposed re-test period.
- 24 month real time stability data for the drug product will be sent as soon as available. (Has been fulfilled post-approval).
- The ongoing studies should be continued, at least up to the shelf life granted (30 months). The results should be submitted after termination of the study or sooner if significant changes occur.

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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RH	Relative Humidity
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/838/ 001/IB/ 001	IB	12-7-2007	11-8-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/838/ 001/IA/ 002	IA	1-4-2008	15-4-2008	Non-Approval	N
Change in the name and/or address of the marketing authorisation holder.	NL/H/838/ 001/IA/ 003	IA	19-5-2008	2-6-2008	Approval	N
Change in the name of the medicinal product.	NL/H/838/ 001/IB/ 004	IB	15-5-2008	14-6-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/838/ 001/IA/ 005	IA	19-5-2008	2-6-2008	Approval	N
Addition of drug substance manufacturer.	NL/H/838/ 001/II/ 006	II	1-8-2008	30-9-2008	Approval	N
Change in the name and/or address of the marketing authorisation holder.	NL/H/838/ 001/IA/ 007	IA	15-12-2008	29-12-2008	Approval	N
Change in the name and/or address of the marketing authorisation holder.	NL/H/838/ 001/IA/ 008	IA	14-1-2009	28-1-2009	Approval	N
Data has been submitted to fulfil one of the post approval commitments. Stability data for drug product up to 24 months have been provided.	NL/H/838/ 001/PAC	Post-approval commitment	12-8-2008	5-3-2009	Approval	N
Change in the name of the medicinal product.	NL/H/838/ 001/IB/ 009	IB	9-4-2009	9-5-2009	Approval	N
Renewal of the marketing authorisation.	NL/H/838/ 001/R/ 001	Renewal	15-2-2010	1-10-2010	Approval	Y, Annex I
Change in the name and/or address of the marketing authorisation holder.	NL/H/838/ 001/IA/ 010/G	IA/G	20-7-2010	19-8-2010	Approval	N

Annex I – NL/H/838/001/R/001 – Renewal of the marketing authorisation

I RECOMMENDATION

Based on the review of the data submitted for this renewal application and on the responses from the MAH to the questions raised by the RMS and CMC, the RMS is of the opinion that the benefit/risk balance of Anastrozole Mylan 1mg film-coated tablets, **is positive**.
The RMS therefore recommends the renewal of the Marketing Authorisation for this product. The RMS is also of the opinion that the renewal can be granted with unlimited validity.

II SCIENTIFIC DISCUSSION

II.1 Introduction

The product is indicated for:

- the treatment of advanced breast cancer in postmenopausal women (efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen)
- adjuvant treatment of breast cancer without metastasis in hormone receptor positive postmenopausal women
- adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer who have received 2 to 3 years of adjuvant tamoxifen.

The EU harmonised birth date is 11 August 1995. Anastrozole Mylan 1mg has been first registered in the Netherlands on 3 October 2007. The product has been approved in 19 countries and is currently marketed in 6 countries, i.e. Slovakia, Czech Republic, Portugal, Spain, Greece and Hungary.
The defined daily dose was assessed as 1 mg taken from the WHO Collaborating Centre for drug statistics methodology. This represents a potential patient exposure of **1265** patient-treatment years (daily doses/365 days).

Anastrozole takes part in the PSUR synchronisation project of the Heads of Medicines Agencies. A CSP (core safety profile) for this active substance has been recently determined after the work sharing procedure UK/H/PSUR/0046/001.
The product informations (SPC and package leaflet) for Anastrozole Mylan 1 mg film-coated tablets has been revised in line with the agreed CSP for anastrozole.

II.2 Module 1/GMP compliance statements

GMP compliance
For the manufacturing site outside the Community the manufacturer of the dosage form a copy of a recent GMP certificate (No.: WEL/181209/5GMP-NAT), issued by the German inspectorate on the 18th December 2009 following an inspection on the 16th of February 2009, has been provided.

For manufacturing sites located within the Community: (dosage form and batch release), copies of recent manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites have been provided.

<u>GMP active substance</u>
An active substance Master File is used.
the manufacturer Synthon B.V., have provided declarations of responsibility for the GMP compliance for starting material, on behalf of the QPs of the bulk drug product manufacturing sites and the QPs of the manufacturing sites responsible for the release of the package product to the market.

Details of contact person for pharmacovigilance, contact person with the overall responsibility for product defects and recalls, and contact person for scientific service in charge of information about the medicinal product, respectively, have been provided.

II.3 Quality

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (version November 2008) a quality expert statement has been submitted for Anastrozole Mylan 1 mg film-coated tablets **(NL/H/0838-0839/001/R/001)** confirming that:

- All changes relating to the quality of the product have been made following applications for variations and that the product conforms to current CHMP Quality guidelines.
- The specifications of the active substance, CASS.NUS.00876_1.0, and those of the finished products, Anastrozole 1 mg film-coated tablets CFPS.NUS.ANA.tab1.001.03, are the currently authorised release specification documents.
- The qualitative and quantitative composition of the finished product corresponds to the active substance and excipients of the product Anastrozole 1 mg film-coated tablets as currently authorised.

The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

A list of all variations submitted since grant of the Marketing Authorisation was provided. A chronological list of follow-up measures/post-authorisation commitments was also provided.

Fulfilled post-approval commitments

The commitment "*24 month real time stability data for the drug product will be sent as soon as available",* has been fulfilled during the renewal. Updated stability data up to 36 months is provided for the anastrozole 1mg film coated tablets (3 batches). The tablets were stored at 25°C/60%RH, 30°C/65%RH, and 40°C/75%RH (12 months) in PVC/PE/PVDC/AL blisters. Results with respect the product stored at 25°C, the water content, dissolution, impurities and microbial contamination remained stable over time. No specific patterns or changes were noted. Results with respect to assay did comply with the specification, at 36 months an assay value of 95.0% was noted for one batch. For the product stored at 30°C, similar results were noted. The results remained stable over time, no out of specifications were noted. At accelerated conditions, no patterns or specific changes were noted; results remained within the acceptance criteria. Based on the provided data, a end of shelf-life of 30 months (as proposed) is considered acceptable.

Results for the tablets packed in the HDPE bulk container stored at 25°C/60%RH and 30°C/65%RH for 24 months (three batches) are also provided. Results showed that the product remained stable for 24 months; the study has been completed at this point. Tablets packed in bulk can be kept for a period of 24 months.

Photostability studies are performed as per European guidelines; results show no degradation after exposure to light. The storage condition '*This medicinal product does not require any special storage conditions*' remains valid.

In addition, the commitment "*The ongoing studies should be continued, at least up to the shelf life granted (30 months). The results should be submitted after termination of the study or sooner if significant changes occur*" has been fulfilled.

II.4 Clinical Efficacy and Safety

II.4.1 Clinical Efficacy

The clinical expert statement, as part of the product license renewal dossier is adequate.

II.4.2 Clinical safety

Summary of the cumulative experience from 1 January 2005 – 26 May 2009
The product has been approved in 19 countries is currently marketed in 6 countries, i.e. Slovakia, Czech Republic, Portugal, Spain, Greece, Hungary.

Three studies with the anastrozole products of Mylan Inc have been performed or analysed during the reporting period of 01 July 2007 – 31 August 2009, involving respectively 34, 36 and 20 patients, both male and female.

The defined daily dose was assessed as 1 mg taken from the WHO Collaborating Centre for drug statistics methodology. This represents a potential patient exposure of **1265** patient-treatment years (daily doses/365 days).

In the Clinical Expert Statement the MAH states that no new pre-clinical or clinical data are available that changes the benefit/risk evaluation for the drug. The Reference Safety Information (RSI) stated in the PSUR reflects the current state of knowledge about the drug appropriately. Thus, the product can be safely renewed for an unlimited period.
The clinical expert statement, as part of the product license renewal dossier is adequate.

In the clinical expert statement no new conclusions have been drawn other from those presented in the PSURs. The general risk-benefit ratio remains positive for the product.

Report of Post Marketing Experience (01 July 2007 – 31 August 1995)
The MAH has submitted a license renewal application through the Mutual Recognition Procedure with the Netherlands acting as Reference Member State.

I Reviewed period

As part of the license renewal application the MAH submitted the following documents:

- PSUR covering the period 01 July 2007 – 31 August 2009,
- Clinical Expert Statement, dated 22 October 2009, and signed
- The approved SPC in English and Dutch. No changes to the SPC are suggested.

This is the first renewal application for the product.

II Actions taken for safety reasons

No specific actions for safety reasons have been taken to date, either by the regulatory authorities or by the market authorisation holders of the anastrozole products within Mylan Inc.

III Changes to the Reference safety information

A worksharing procedure with the UK as pRMS (UK/H/PSUR/0046/001) released the final assessment report and the resulting Core Safety Profile for anastrazole INN on the 14th of May 2010.
On request of the RMS, the SmPC and PL for Anastrozole Mylan 1 mg were brought in line with the agreed CSP for Anastrozole.

IV Adverse reactions

A total of 15 ICSRs on anastrozole have been identified during the period of this report. These ICSRs contained a total of 54 ADRs. These were obtained from the worldwide scientific literature (4) and Regulatory Authorities (11). There were no reports from clinical trials.
All these 15 cases were regarded as unlisted (8 serious and 7 non-serious).

	Serious		Non-Serious		Total
	Listed	Unlisted	Listed	Unlisted	
HCP	0	8	0	7	15
Non-HCP	0	0	0	0	0
Total	**0**	**8**	0	**7**	**15**

The following adverse events were considered serious and unlisted:

Years / Sex	Adverse Event	Comments
65, female	Palpitations, tremor, felt faint, dizziness, appetite loss	-
69, female	Vision abnormal, dizziness, disequilibrium, concentration impaired	-
59, female	Oesophageal pain, chest pressure, agitation and cephalgia	-
57, female	Sensation of pressure, vaginal bleeding and pelvic pain	-
67, female*	Primary uterine rhabdomyosarcoma	Past therapies also included tamoxifen.
60, females	Bipolar disorder, pain in extremity, suicidal ideation, tremulousness	Positive dechallenge
78, female	Oedema perpheral, Abdominal distension, Pruritus, Skin exfoliation	-
51, female	Chest pain, urticaria, hyperhidrosis, tremor, salivary hypersecretion	-

*** fatal cases**

Most of the serious adverse events were reported only once during the review period. Based on the case reports received no actions seem necessary at this moment.

V Studies

Three studies in healthy volunteers have been undertaken with anastrozole during the period of the report:
Title: Single-Dose Fasting Bioequivalence Study of Anastrozole Tablets (1 mg; Mylan) and Arimidex Tablets (1 mg; AstraZeneca) in Healthy Female (Not of Childbearing Potential) Volunteers
No. of Subjects: 34
Country: Canada

Title: Single-Dose Fasting Bioequivalence Study of Anastrozole Tablets (1 mg; Mylan) and Arimidex Tablets (1 mg; AstraZeneca) in Healthy Female (Not of Childbearing Potential) Volunteers
Country: USA
No. of Subjects: 36, of which 35 completed the study

Title: Single-Dose Fasting Bioequivalence Study of Anastrozole Tablets (1 mg; Genpharm) and ArimidexTablets (1 mg; AstraZeneca) in Healthy Male and Female (Not of Childbearing Potential) Volunteers
Country: USA
No. of Subjects: 20

There were no serious adverse events or important safety findings in any of the above mentioned studies.

VI Targeted new safety studies planned, initiated or continued during the reporting period

None.

VII Published studies

No published safety studies of interest were identified.

VIII Efficacy related information, Late breaking information, Drug interaction, Overdose, Drug Abuse, Pregnancy and Lactation, Special Patient Groups, Effects of Long Term Treatment, Medication Errors

No new safety information has been identified with regard to the above mentioned topics.

Conclusion on Safety
Overall, 15 case reports comprising 54 ADRs were received during the period of the PSUR covering the period 01 July 2007 – 31 August 2009. 8 cases were regarded as serious including one fatal case. There were no reports from clinical trials. No new safety issues were identified based on spontaneous reports, literature or published studies.

Anastrozole takes part in the PSUR synchronisation project of the Heads of Medicines Agencies. The next PSUR should cover the period from 01 September 2009 to 31 August 2012 and should be submitted within 60 days from the data lock point, i.e. October 2012.

III PRODUCT INFORMATION

III.1 Summary of Product Characteristics

The revised SmPC has been brought in line with the agreed CSP for Anastrozole, as requested by the RMS during the clock stop period. Additionally, typographical errors have been corrected.

The RMS considers the proposed revised SPC (enclosed) acceptable.

III.2 Package leaflet and user testing

Package Leaflet
In view of the changes proposed in the SmPC, the PIL has also been updated.
The RMS considers the proposed revised PIL (enclosed) acceptable.

Assessment of User Testing
Assessment of the user testing was carried out during the DCP procedure NL/H/0833/001/DC (finilised on 10-02-2007).

III.3 Labelling

No changes to the labelling were proposed.

IV REMAINING POST-APPROVAL COMMITMENTS TO BE FULFILLED BY MAH

The following post-approval commitments are still outstanding:

Area	Description	Due date
Pharmacovigilance	The next PSUR should be submitted after 3 years	October 2012.
Quality 1	The MAH commits itself to perform a method transfer from Quinta to any of the other mentioned testing sites before this site will be used as a testing site.	Ongoing
Quality 2	The MAH commits to the stability testing of the drug substance continuing throughout the proposed re-test period.	Ongoing

V OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

Based on the data accumulated during the review period, the benefit/risk ratio for the product remains favourable. There have been no new safety issues identified in the period under review. The RMS is of the opinion that the renewal can be granted with unlimited validity.

The SPC contains adequate information and it has been aligned to the recently agreed CSP for Anastrozole.

In view of the changes proposed in the SmPC, the PIL has also been updated.

The MAH should submit PSURs at 3 yearly intervals with a data lock point no more than 60 days before submitting the PSUR.
The next PSUR should cover the period from 01 September 2009 to 31 August 2012 and should be submitted within 60 days from the data lock point, i.e. October 2012.

List of abbreviations

ADR Adverse Drug Reactions
CSP Core Safety Programme
ICSR Individual case Safety Report