CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Anastrozol Synthon 1 mg, film-coated tablets
Synthon 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/833/01/DC
Registration number in the Netherlands: RVG 34003

Date of first publication: 30 November 2007
Last revision: 20 January 2011

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, EE, EL, ES, FI, FR, HU, IE, IS, LT, LU, LV, NO, PL, PT, SI, SK
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 Synthon 1 mg, film-coated tablets, from Synthon B.V. 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 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 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 Synthon 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. The shelf-life has been changed into 48 months (as packaged for sale, supported by real time data) by a post-approval variation. See table '*Steps taken after finalisation of the initial procedure*' variation NL/H/833/001/IB/007.

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 MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Anastrozol Synthon, 1 mg tablets (Synthon 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 24 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 Synthon 1 mg tablet and reference Arimidex 1 mg tablet 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 Synthon, 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 Synthon, 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/833/ 001/IB/ 001	IB	12-7-2007	13-8-2007	Approval	N
Change in the name of the medicinal product in Greece.	NL/H/833/ 001/IB/ 002	IB	13-5-2008	12-6-2008	Approval	N
Addition of drug substance manufacturer.	NL/H/833/ 001/II/ 003	II	1-8-2008	30-9-2008	Approval	N
Change in the name of the medicinal product in Portugal.	NL/H/833/ 001/IB/ 004	IB	17-7-2008	16-8-2008	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/833/ 001/PAC	Post-approval commitment	12-8-2008	5-3-2009	Approval	N
Change in the name of the medicinal product in Finland.	NL/H/833/ 001/IB/ 005	IB	10-7-2009	9-8-2009	Approval	N
Change in the name of the medicinal product in EE, LT, and LV.	NL/H/833/ 001/IB/ 006	IB	10-7-2009	9-8-2009	Approval	N
Change in the shelf-life or storage conditions of the finished product. Extension of the shelf-life of the finished product, as packaged for sale (supported by real time data).	NL/H/833/ 001/IB/ 007	IB	6-4-2010	6-5-2010	Approval	N
Renewal of the marketing authorisation.	NL/H/833/ 001/R/ 001	Renewal	17-5-2010	23-11-2010	Approval	Y, Annex I

Annex I – NL/H/833/001/R/001- Renewal of the marketing authorisation

I RECOMMENDATION

Based on the review of the data submitted for this renewal application, the RMS is of the opinion that the benefit/risk balance of Anastrozol Synthon 1mg, film-coated tablets, **is positive.**
The RMS therefore recommends the renewal of the Marketing Authorisation for Anastrozol Synthon 1mg.
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:

- 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 postmenopausal women with hormone receptor positive early invasive breast cancer.
- Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

The EU harmonised birth date is 11 August 1995. Anastrozol Synthon 1mg (NL/H/833-845-846-849-850-851/01/DC) has been first registered in the Netherlands on 03 October 2007. The product has been approved in 23 countries and is currently marketed in 2 countries, i.e. Portugal and Greece.
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 12,288,998 patient-days. The average treatment length for which patients used anastrozole during the period of this report is unknown. However, it is known that patients starting treatment with anastrozole will continue treatment for a prolonged period of time. If one assumes that once a patient starts taking anastrozole the patient does not stop treatment until today; one can calculate the number of patients currently using Synthon B.V. anastrozole or Genthon anastrozole.
This calculation is: the total amount of anastrozole sold by Synthon BV and Genthon BV (12,288,998 mg), divided by the DDD (1 mg), divided by the number of days covered in this report (845 days). In this manner, it is calculated that 14,543 patients are currently using Synthon BV and Genthon BV anastrozole.
It is estimated that around 14,543 patients were treated with anastrozole, from 10 May 2007 through 31 Aug 2009.
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, finilised on 14/05/2010.
On request of the RMS, the product information (SPC and package leaflet) for Anastrozole Synthon 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 GMP certificate (No.: WEL/181209/5GMP-NAT) issued by the German inspectorate on the 18th December 2009 after inspection of the site on 16/02/2009, was 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.

GMP active substance
An active substance Master File is used.

The Qualified Persons (QPs) of 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 Synthon 1 mg film-coated tablets 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 EFPS.NUS.ANA.tab1.001 (4.0), 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 product with the qualitative and quantitative composition have been provided and are also attached to this report.

II.4 Clinical Safety

II.4.1 Summary of Cumulative Experience (10 May 2007 – 26 May 2009)

The product has been approved in 22 countries is currently marketed in 2 countries, i.e. Portugal and Greece.

In the Clinical Expert Statement the MAH states that:

- No new (pre-clinical or clinical) data are available which changes or results in a new benefit-risk evaluation.
- The product can be safely renewed at the end of a 5-year period for an unlimited period.
- The authorities have been kept informed of any additional data significant for the assessment of the benefit/risk ratio of the product concerned.

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

II.4.2 Report of Post Marketing Experience (10 May 2007– 31 August 2009)

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 10 May 2007 – 31 August 2009,
- Clinical Expert Statement, dated 20 October 2009, and signed
- Currently approved SPC in English,
- Proposed SPC in English. Changes to the SPC are suggested.

This is the first renewal application for the product.

Synthon BV obtained approval for a large number of Decentralised Procedures (DCPs) for Anastrozole 1 mg film-coated tablets, in The Netherlands on 10 May 2007. For a number of these DCPs the marketing authorisation holder (MAH) in the Reference Member State (RMS) has been transferred in 2008 and 2009, from Synthon BV to commercial partners. These DCPs are no longer part of the scope of this PSUR.
An overview of the Anastrozole DCPs for which Synthon BV or Genthon BV are the MAH in the RMS is given in the following table. This PSUR covers all these DCPs.

DCP	MAH-RMS
NL/H/833/01/DC	Synthon BV
NL/H/845/01/DC	Synthon BV
NL/H/846/01/DC	Synthon BV
NL/H/850/01/DC	Synthon BV
NL/H/849/01/DC	Synthon BV
NL/H/851/01/DC	Genthon BV*

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 1 mg film-coated tablets.

III Changes to the Reference safety information

The summary of product characteristics (SPC) currently approved for all DCPs in English has been used as reference safety information.
A CSP (core safety profile) for this active substance has been recently determined after the work sharing procedure UK/H/PSUR/0046/001, finilised on 14/05/2010.
On request of the RMS, the product information (SPC and package leaflet) for Anastrozole Synthon 1 mg film-coated tablets has been revised in line with the agreed CSP for anastrozole.

IV Adverse reactions

A total of 47 ICSRs (two spontaneous and 45 literature) comprising 83 ADRs/AEs have been identified during the period of this report. Twenty-three of the 47 ICSRs were serious, 24 were non-serious. Three ICSRs had a fatal outcome. There were no ICSRs from clinical studies and regulatory authority.

The following ICSRS reported a fatal outcome:

- 78-year-old female with concomitant history of hypertension and heart murmur experienced a myocardial infarction while taking anastrozole.
- 67-year-old female with a history of breast cancer and gastrointestinal stromal tumor developed a primary uterine rhabdomyosarcoma.
- A 73-year-old female with a history of hypertension, diabetes mellitus and coronary artery disease developed acute renal failure and died eight months after diagnosis of sclerosing glomerulonephritis. Treatment also included perindopril which was thought to be the reason of sclerosing glomerulonephritis.

The following adverse events were considered serious and unlisted:

Adverse Event	**Number**
Myocardial infarction*	1
Conjunctival hyperaemia	1
Retinal artery occlusion	1
Retinal haemorrhage	4
Gastritis	1
Malaise	1
Oedema peripheral	1
Hepatotoxicity	1
Myalgia	1
Angiosarcoma	1
Malignant neoplasm progression	1
Metastatis	1
Rhabdomyosarcoma*	1
Burning sensation	1
Carpal tunnel syndrome	2 (+ 2 non-serious cases)
Neuralgia	2
Paraesthesia	1
Glomerulonephritis	1
Renal failure acute*	1
Obliterative bronchiolitis	4
Cutaneous erythematosus	1
Cutaneous vasculitis	1
Periorbital oedema	1

*** fatal cases**

Myocardial infarction, retinal haemorrhage, drug interaction with perindopril and obliterative bronchiolitis will be closely monitored.

Carpal tunnel syndrome
Four ICSRs were collected regarding this ADR. All patients had estrogen receptor positive breast cancer and they used anastrozole for at least one month before the experienced *Carpal tunnel syndrome*. All patients were menopausal or had bilateral oophorectomies and hysterectomy when
diagnosed with breast cancer.
- Two patients had improvement of the symptoms after switching to tamoxifen.
- One patient had improvement of the symptoms after changing to conservative therapy.
- One patient experienced minimal improvement with tamoxifen and finally underwent a surgical decompressive procedure.

Besides *Carpal tunnel syndrome*, neuropathic pain, paraesthesia, trigger finger and morning stiffness were experienced.
One study was collected regarding this ADR. The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial investigated the use of aromatase inhibitors in postmenopausal women. *Carpal tunnel*

syndrome was reported in 78 anastrozole users (3%) compared to 22 tamoxifen users (1%). This difference in incidence was significant (p<0.0001).
Carpal tunnel syndrome is listed in the Arimidex® SPC as a common ADR. Based on the collected safety information, it is recommended to include *Carpal tunnel syndrome* in the SPC.

Previous comment:
Based on the safety data collected for this PSUR the MAH recommended that 'carpal tunnel syndrome' should be included in the SPC. This is accepted. However, before the current SPC is changed the final CSP (core safety profile) from the worksharing procedure with the UK as the pRMS should be awaited. See above. Monitoring of myocardial infarction, retinal haemorrhage, drug interaction with perindopril and obliterative bronchiolitis is accepted.

Day 60 comment:
The SPC has been brought in line with the agreed CSP for Arimidex. Point resolved

V Studies

No studies have been newly analysed.

VI Targeted new safety studies

None.

VII Published studies

Cuzick, J. 2007.The ATAC trial: the vanguard trial for use of aromatase inhibitors in early breast cancer. *Expert Rev Anticancer Ther 7(8)*: 1089-94
The Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial was the first trial to explore the use of aromatase inhibitors in postmenopausal women with early breast cancer and is the largest published cancer treatment trial in breast cancer. The main results have been published at 33-, 47- and 68- months median follow-up and further analyses are planned for the end of 2007 and in 2010. This trial demonstrated that five years of treatment with anastrozole was generally better tolerated than five years of treatment with tamoxifen, and led to lower recurrence rates, especially in receptor-positive women (26% reduction). The side-effect profile was different from that for tamoxifen, with fewer hot flushes, gynecologic symptoms, endometrial cancers, strokes and thromboembolic events; however, an increased incidence of fractures, joint symptoms and carpal tunnel syndrome was observed for the incidence of predefined adverse events. Future analyses will determine whether benefits and fracture rates persist after stopping treatment, and the extent to which currently marginal benefits on late end points, such as distant recurrence and death after recurrence, are sustained or improved.

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.

II. 4.2.3 Conclusion on Safety

Overall, 47 ICSRs (two spontaneous and 45 literature) comprising 83 ADRs/AEs have been identified during the period of this report. Twenty-three of the 47 ICSRs were serious, 24 were non-serious. Three ICSRs had a fatal outcome. There were no ICSRs from clinical studies and regulatory authority.
The current SPC has been brought in line with the final CSP (core safety profile) from the work sharing procedure UK/H/PSUR/0046/001.
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, and amended a according to RMS and CMS comments.

The RMS considers the proposed revised SPC, version: M1.3.5_01.ANA.tab1.001.09 and dated 22-10-10, acceptable.

III.2 Package leaflet and user testing

Package Leaflet
The revised PL, has been brought in line with the agreed CSP for Anastrozole and it has been amended a according to RMS and CMS comments.

The RMS considers the proposed revised PL, version: M1.3.5_03.ANA.tab1.001.09 and dated 22-10-10, acceptable.

Assessment of User Testing
Assessment of the user testing was carried out during the DCP procedure NL/H/833/001/DC; finilised on 10/02/2007.

III.3 Labelling

The labelling texts have been amended according to comments from the CMS.
The RMS considers the proposed revised labelling texts, version: M135-02.ANA.tab1.001.05 and dated 14-07-10 are acceptable.

IV REMAINING POST-APPROVAL COMMITMENTS TO BE FULFILLED BY MAH

The following post-approval commitments are still outstanding:

Area[1]	Description	Status	Due date[2]
Pharmacovigilance	The next PSUR should be submitted after 3 years	-	October 2012.
Quality 1	A method transfer from Quinta to any of the other mentioned drug substance testing sites before this site will be used as a testing site	Not fulfilled. Pending	Before this site will be used as a testing site
Quality 2	Stability testing of the drug substance should continue throughout the proposed re-test period.	Not fulfilled.	Pending.

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 has been aligned to the recently agreed CSP for Anastrozole and amended according to RMS and CMS comments. The proposed SPC is acceptable.
The PIL and labelling have been also updated (brought in line with SPC). The proposed PL and labelling texts are acceptable.

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
ATAC	Anastrozole, Tamoxifen, Alone or in Combination
CSP	Core Safety Programme
ICSR	Individual case Safety Report