CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Anastrozol Regiomedica 1 mg film-coated tablets Regiomedica GmbH, Germany

anastrozol

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/1499/001/DC
Registration number in the Netherlands: RVG 103523

1 April 2010

Pharmacotherapeutic group:	hormone antagonists and related agents; enzyme inhibitors
ATC code:	L02BG03
Route of administration:	oral
Therapeutic indication:	advanced breast cancer in postmenopausal women; hormone receptor positive early invasive breast cancer in postmenopausal women (adjuvant); early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen (adjuvant).
Prescription status:	prescription only
Date of authorisation in NL:	21 December 2009
Concerned Member States:	Mutual recognition procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1).

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

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Anastrozol Regiomedica 1 mg film-coated tablets, from Regiomedica GmbH. The date of authorisation was on 21 December 2009 in the Netherlands. The product is indicated for:

- Treatment of advanced breast cancer in postmenopausal women. The efficacy of anastrozole has not yet 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.

A comprehensive description of the indications and posology is given in the SPC.

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, oestradiol is produced primarily from the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues. Oestrone is subsequently converted to oestradiol. Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer. Using a highly sensitive assay method, it was demonstrated in postmenopausal women that anastrozole at a daily dose of 1 mg reduces the oestradiol level by more than 80%. Anastrozole has no progestogenic, androgenic or oestrogenic effect. Daily doses of anastrozole of up to 10 mg have no effect on cortisol or aldosterone production, measured before and after an ACTH challenge test. Corticoid supplements are therefore not required.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Arimidex 1 mg film-coated tablets (NL RVG 19123) which has been registered in Sweden since 1996 by Astra Zeneca (original product). In the Netherlands, Arimidex has been registered since 1996 by a national procedure. 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 MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Arimidex 1 mg film-coated tablets, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

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

Active substance
The active substance is anastrozole, an established active substance which is not described in the Ph. Eur.* or any other pharmacopoeia. Anastrozole is a white to off-white powder, freely soluble in most organic solvents, slightly soluble in water and insoluble in n-hexane. Anastrozole is not hygroscopic under humid conditions. It has no isomers and no polymorphic forms.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The manufacturing process of anastrozole consists of 3 main steps which are adequately described. In the last stage, anastrozole is purified and micronised. No class 1 solvents or heavy metal catalysts are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH, with additional requirements for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 1 pilot scaled and 3 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 1 pilot-scale batch and 3 full-scale batches stored at 25°C/60% RH (36 months for pilot-scale batch and 18 months for full-scale batches) and 40°C/75% RH (6 months). The batches were adequately stored. Anastrozole is considered to be photostable.
The proposed retest period of 30 months without additional storage requirements is justified.

** 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.*

Medicinal Product

Composition
Anastrozol Regiomedica 1 mg film-coated tablets are packed in either clear PVC/PVDC/Al-blister packs enclosed in an outer carton or in a white HDPE tablet container with a white PP child resistant screw cap. Anastrozol Regiomedica 1 mg film-coated tablets contain as active substance 1 mg of anastrozole.

Anastrozol Regiomedica 1 mg are white to off-white, round, film-coated, biconvex tablets engraved with "*A 1*" on one side and plain on the other.
The excipients are:
Tablet core - lactose monohydrate, povidone (K30) (E1201), sodium starch glycolate (type A), magnesium stearate (E572).
Tablet coating - hypromellose (E464), titanium dioxide (E171), macrogol 400.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were in respect to the compatibility of the drug substance with the excipients, the manufacturing process development and comparison of dissolution profiles with the originator product. The composition and manufacturing process of the drug product batch used in the BE studies is similar to the final drug product. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Dissolution
Bioequivalence studies were performed with generic anastrozole 1 mg tablets versus originator Arimidex from the French market. The generic biobatch was manufactured according to the proposed manufacturing process. Originator Arimidex 1 mg tables sourced from different countries were compared in terms of appearance, qualitative composition, dissolution profiles (5 time points: 5, 10, 15, 30, 45 minutes) and impurity profiles.
The dissolution profiles of the originator product from all the concerned member states show a dissolution of more than 85% in 15 minutes and are concluded to be similar to each other and to the French reference product. The applicant has sufficiently shown that dissolution is pH independent.

Manufacturing process
The manufacturing process consists mainly of granulation, blending, tablet compressing and coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented on three production scale batches.

Excipients
Except for the Opadry White film-coating suspension, the excipients comply with the Ph.Eur. The components of Opadry White comply with the Ph.Eur. The specifications and analytical procedures for Opadry White have been described adequately. All specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, hardness, thickness, diameter, average tablet mass, assay, uniformity of dosage units, related substances, dissolution and microbial limits. Except for hardness, the release and shelf-life requirements are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production scale batches, demonstrating compliance with the release specification.
The MAH has committed to provide stability data for two additional production scale batches packed in both blisters and bottles at the end of their shelf-life.

Stability of drug product
Stability data on the product has been provided on two pilot-scale batches and one smaller batch, stored at 30°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC/Al-blisters and HDPE tablet containers. No changes are seen under both conditions. Based on the submitted data, the proposed shelf-life of 3 years without any additional storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The magnesium stearate used in this formulation is derived from vegetable origin. 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.

II.2 Non clinical aspects

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

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

II.3 Clinical aspects

Anastrozol 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 Regiomedica 1 mg film-coated tablets (Regiomedica GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Arimidex 1 mg film-coated tablets (Astra Zeneca, France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.

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

Study design
A single-dose, randomised, two-way, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male volunteers, aged 18-55 years. Each subject received a single dose (1 mg) of one of the 2 anastrozole formulations. The tablet was orally administered with 240 ml water after an overnight (10 hour) fast. Water was provided *ad libitum* until 1.0 hour pre-dose and from 1.0 hour post-dose. A standard meal was provided at 5.0 and 10.0 hours post-dosing. All meals were free of grapefruit products and caffeine. All meals consisted of a medium sized serving of meat, vegetables, starch and fruit. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 32, 48, 72, 96, 120, 152 and 216 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Anastrozole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of anastrozole. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results
During this study, five subjects experienced adverse events. These consisted of headache (1 episode), itchy rash on inner arms (I episode), nausea (1 episode), pain at canula site (1 episode), rash type small lumps on both inner arms (1 episode), skin breakout (pimples) (1 episode) and sore throat (1 episode). Except for the episodes of pain at the cannula site and pimples, which were deemed "not related" to the study medication, these are generally recognised possible side effects of anastrozole. All AE's were mild at onset. All 26 subjects completed the study and therefore were eligible for pharmacokinetic analysis.

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

Treatment N=26	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	656 ± 157	686 ± 177	14.29 ± 2.23	1.3 (0.5 – 3.5)	45.9 ± 8.9
Reference	668 ± 166	698 ± 185	14.09 ± 2.56	1.4 (0.5 – 3.5)	44.7 ± 9.2
***Ratio (90% CI)**	0.98 0.95 – 1.01	0.98 0.95 – 1.01	1.01 0.98 – 1.05	---	---
CV (%)	20	22	14	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of anastrozole under fasted conditions, it can be concluded that Anastrozol Regiomedica 1 mg film-coated tablets and Arimidex 1 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil 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, 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 postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The participants were mainly women on the age of 48 to 70 years. The questionnaire consisted of 14 open questions on safety and usage of the medicine and one question on the general impression on the package leaflet. The questionnaire addressed relevant safety issues. No amendments were made between round 1 & 2. According to the results, more than 90% of the participants could locate the information and could answer the questions correctly. Relevant recommendations for improvement were implemented in the final tested PIL.

The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Anastrozol Regiomedica 1 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Arimidex 1 mg film-coated tablets. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Anastrozol Regiomedica 1 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 September 2009. Anastrozol Regiomedica was authorised in the Netherlands on 21 December 2009.

A European harmonised birth date has been allocated (11 August 1995) and subsequently the first data lock point for anastrozole is August 2012. The first PSUR will cover the period from September 2009 to August 2012, after which the PSUR submission cycle will be 3 years.

The date for the first renewal will be: September 2014.

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

Quality - medicinal product

- The MAH has committed to provide stability data for two additional production scale batches packed in both blisters and bottles at the end of their shelf-life.

List of abbreviations

ACTH	Adrenocorticotrophic Hormone
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached