CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Anastrozol Ratiopharm 1 mg, film-coated tablets
Ratiopharm Nederland 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/834/01/DC
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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, HU, IT, LU, NO, PL, SE, 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 Ratiopharm 1 mg, film-coated tablets, from Ratiopharm Nederland 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(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 Ratiopharm 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/834/001/IB/004.

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 Ratiopharm, 1 mg tablet (Ratiopharm Nederland B.V.) 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.
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.

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.

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 Ratiopharm 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 Ratiopharm, 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 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 Ratiopharm, 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/0834 /001/IB/ 001	IB	24-9-2007	24-10-2007	Approval	N
Repeat-use procedure with EE, LT, and LV.	NL/H/0834 /001/E/ 001	E	7-3-2008	5-6-2008	Approval	Y, Annex I
Addition of drug substance manufacturer.	NL/H/0834 /001/II/ 002	II	1-8-2008	30-9-2008	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/834/ 001/PAC	Post-approval commitment	12-8-2008	5-3-2009	Approval	N
• Deletion of a pack size for the finished product. • Change in the name and/or address of the marketing authorisation holder.	NL/H/0834 /001/IA/ 003/G	IA/G	19-5-2010	18-6-2010	Approval	N
Extension of the shelf life of the finished product, as packaged for sale (supported by real time data).	NL/H/0834 /001/IB/ 004	IB	19-5-2010	18-6-2010	Approval	N

Annex I - Repeat-use procedure - Variation NL/H/0834/001/E/001

The Repeat use procedure started on 7 March 2008. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states (EE, LT, and LV), on the basis of the data submitted, considered that essential similarity has been demonstrated for Anastrozol Ratiopharm, 1 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 5 June 2008.

The Data Lock Point is August 2009, and the first PSUR is to be submitted on October 2009. The PSUR submission cylce is 3 years.

The date for the first renewal will be: 10 May 2010.

The following post-approval commitments have been 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.
- 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.