IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Anastrozole 1 mg Film-coated tablets
Anastrozole
PA0074/068/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for a generic version of Anastrozole, under various trade names. The product is indicated for the treatment of

- Advanced breast cancer in Hormone receptor positive postmenopausal women
- 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 Summary of Product Characteristics (SmPC).

The active substance is anastrozole, which is an orally active reversible aromatase inhibitor. In postmenopausal women the aromatase enzyme converts the sex hormones androstenedione and testosterone, into oestrogen. Anastrozole prevents this conversion by blocking the action of the aromatase enzymes, thus causing oestrogen levels in the body to fall. Anastrozole has been shown to have significant benefit in the treatment of postmenopausal women with early and advanced breast cancer.The recommended dosage is one tablet (1 mg) once a day.

This is a generic application claiming essential similarity with the the reference product Arimidex 1mg 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 is 'abridged' as it refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorised reference medicinal product. No new pre-clinical and clinical efficacy studies were conducted, which is acceptable for this abridged application.

To support the application, the applicant has submitted a report of one bioequivalence study.
The bioavailability of the proposed anastrozole 1mg (Unichem Laboratories, Batch No. S0007(A) was compared to the reference product Armidex 1mg(AstraZeneca, UK Lot No. EG418).

II. QUALITY ASPECTS

II.1 Introduction

Anastrozole is a non-steroidal aromatase inhibitor. The proposed product is in the form of a white, round, biconvex film-coated tablet containing 1mg of anastrozole active substance.

II.2 2.2 Drug Substance

II.2 Drug substance

The active substance is anastrozole, an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal Product

P.1 Composition

The finished product consists of a tablet core containing 1mg of the active substance anastrozole along with the excipients lactose monohydrate (equivalent to 90.3mg of lactose), magnesium stearate and sodium starch glycolate and is coated with a film coat containing polyvinyl alcohol- partially hydrolysed, Macrogol 3350, talc and titanium dioxide.

P.2 Pharmaceutical Development

The product which is an immediate release film coated tablet, is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated for the proposed batch size.

P.4 Control of Other Substances (Excipients*)*

All ingredients as described in P.1 above comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as clear transparent blisters of PVC/PVDC film heat sealed to aluminium foil packaged in a carton.

Statements have been provided that the PVC/PVDC film complies with Ph. Eur. Monograph 3.1.11 and 3.2.2 and EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years with a storage recommendation of 'no special storage conditions' proposed.

No TSE risk materials are used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Anastrozole 1mg film coated tablets.

III. NON-CLINICAL ASPECTS

I.1 Introduction

As this was a generic application, no new animal studies were submitted. Information from the originator product is referenced. The product is intended to substitute for identical products on the market.

IV. CLINICAL ASPECTS

To support the application, the applicant has submitted the report of one bioequivalence study.

The bioavailability of the proposed anastrozole 1mg was compared to the reference product Arimidex 1mg (AstraZeneca). This was a single dose two period cross over study in healthy subjects, under fasted conditions. The study compared the bioavailability and pharmacokinetic profile of the proposed anastrozole with the reference formulation in postmenopausal female subjects.

Results

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

Treatment
Test

Reference

***Ratio (90% CI)**

CV (%)

$AUC_{0-\infty}$ 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

AUC_{0-t} xg/ml/h	**$AUC_{0-\infty}$** xg/ml/h	**C_{max}** xg/ml	**t_{max}** h	**$T_{1/2}$** h
1154+/-271	1207+/-324	22.6+/-3.1	1.25	48.2+/-12.1
1161+/-262	1175+/-1207	21.8+/-2.8	1.50	47.0+/-10.6
99.3 (97.30-101.41)	99.2 (97.06-101.30)	103.3 (100.05 -106.56)		
4.5%	4.6	6.9%		

The 90% confidence intervals for test to reference ratios of Least Mean Squares Means based on In-transformed data for AUC(0-t), AUC(0-inf), C(max) were found within the bioequivalence acceptance range of 80-125%. Based on these results, it can be concluded that test anastrozole (Unichem)1mg and reference Arimidex 1mg tablet(AstraZeneca) are bioequivalent with respect to rate and extent of absorption of anastrozole.

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 readability test has been adequately performed.

Pharmacovigilance System
The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

V. OVERALL CONCLUSIONS

Anastrozole 1mg film coated tablet is a generic form of Arimidex 1mg film coated tablet. Arimidex is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile. On the basis of the data submitted, the HPRA and the other Member states involved in the procedure considered that bioequivalence has been demonstrated for Anastrozole 1 mg with the reference product, and have therefore granted a marketing authorisation.

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 applicant will continue to monitor the stability of this product and results will be made available on request or notified to the competent authorities if any issues arise. Furthermore the applicant is obliged by Article 23 of Directive 2001/83EC as amended, to update this dossier in line with scientific and technical progress on an ongoing basis.

VI. REVISION DATE

November 2012