IPAR

Public Assessment Report

Scientific discussion

Anastrozole Zaphyr Pharmaceuticals 1 mg film-coated tablets (ANASTROZOLE)

This module reflects the scientific discussion for the approval of Anastrozole 1 mg film-coated tablets. The procedure was finalised at D196 – 12/08/2009. For information on changes after this date please refer to the module 'Update'.

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. 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 Arimidex 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 monographed in the European Pharmacopoeia, 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. or equivalent standards.

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.

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 according to the shelf-life and storage conditions detailed in sections 6.3 and 6.4 of the SmPC.

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

III.1 Introduction

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

IV CLINICAL ASPECTS

I. Clinical aspects

To support the application, the applicant has submitted the report of one bioequivalence study.
The bioavailability of the proposed anastrozole 1mg product 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, t_{max} median, range) of anastrozole following single dose under fasting conditions

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h	$T_{1/2}$ h
Test	1154+/-271	1207+/-324	22.6+/-3.1	1.25	48.2+/-12.1
Reference	1161+/-262	1175+/-1207	21.8+/-2.8	1.50	47.0+/-10.6
***Ratio (90% CI)**	99.3 (97.30-101.41)	99.2 (97.06-101.30)	103.3 (100.05-106.56)		
CV (%)	4.5%	4.6	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

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 product 1mg and reference Arimidex 1mg tablet (AstraZeneca) are bioequivalent with respect to rate and extent of absorption of anastrozole . The products can be considered essentially similar and the requirements of Article 10.1 of Directive 2001/83/EC are fulfilled.

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 Zaphyr Pharmaceuticals 1 mg 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 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

VII UPDATES

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
To extend the shelf-life of the finished product to 41 months	IE/H/189/001/IB//005 IE/H/190/001/IB//006	Section 6.3 of SmPC	20th May 2011 22nd March 2012	21st June 2011 21st April 2012	Approval	N

ope	Procedure number	Product Informationaffected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
e Summary of Product aracteristics (SmPC) has been dated in line with the harmonised PC for Anastrazole approved by CHMP(Committee for Human edicinal Products) at the EMA.	IE/H/191/01/IB/03	Update to sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3, 6.5 & 6.6	15/10/2012	14/11/2012	Approval	N

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.