LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Letrozole Bluefish
(letrozole)

SE/H/843/01/DC

This module reflects the scientific discussion for the approval of Letrozole Bluefish. The procedure was finalised at 27 November 2009. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Bluefish Pharmaceuticals AB has applied for a marketing authorisation for Letrozole Bluefish, film-coated tablet, 2,5 mg claiming essential similarity to Femar, film-coated tablet, 2,5 mg marketed in Sweden by Novartis Sverige AB.
The product contains letrozole as active substance. For approved indications see the Summary of Product Characteristics.
The reference product used in the bioequivalence study is Femara, film-coated tablet, 2,5 mg marketed by Novartis Pharma SAS in France.

II. QUALITY ASPECTS

II.1 Introduction

Letrozole Bluefish is presented in the form of film-coated tablets containing 2.5 mg of letrozole . The excipients are lactose monohydrate, microcrystalline cellulose, maize starch, sodium starch glycollate, silica, colloidal, anhydrous, magnesium stearate, film-coating, titanium dioxide, yellow iron oxide, macrogol, red iron oxide, talc, hypromellose and purified water. The *tablets* are packed in blister packages.

II.2 Drug Substance

Letrozole has a monograph in the Ph Eur.

Letrozole is a white or yellowish crystalline powder which is practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in methanol. The structure of letrozole has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Letrozole Bluefish, film-coated tablets is formulated using excipients described in the current Ph Eur, except for yellow and red iron oxides which are controlled according to acceptable in house specifications.. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility and hygroscopic properties.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The application was based on one bioequivalence study. It was a single-dose, randomised, 2-way crossover study in 20 healthy, postmenopausal women under fasting conditions. In each of the two study periods, a single dose of 2.5 mg letrozole was given with 240 ml of water in the morning after a 10-hour fast. Subjects continued fasting for 4 hours after dose. Blood sampling was made pre-dose and for 240 hours post-dose. The treatment phases were separated by a washout period of 21 days. The primary pharmacokinetic parameters were AUC and C_{max} of parent letrozole. Preset criteria for concluding bioequivalence between the test and reference products were 90% geometric confidence intervals of the test/reference ratio of least-squares means from the ANOVA of the ln-transformed letrozole AUC_{0-t} and C_{max} within 80% to 125%. Considering the pharmacokinetic properties of letrozole, the study design and the criteria for bioequivalence are appropriate.

The new letrozole 2.5 mg film-coated tablet (test) was compared with Femara® 2.5 mg film-coated tablet, manufactured by NovartisPharma SAS, France (reference).

Analysis of letrozole concentrations in plasma samples was made using a high performance liquid chromatography / tandem mass spectrometry method.

The pharmacokinetic and statistical results are shown below:

Pharmacokinetic parameters for letrozole (non-transformed values; arithmetic mean ± SD, t_{max} median, range) and 90% CI for test/ref ratio

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1586 ± 375	1689 ± 417	37.0 ± 8.6	1.5 (0.67-5.0)
Reference	1599 ± 381	1701 ± 419	37.8 ± 8.5	1.25 (0.67-3.0)
***Ratio (90% CI)**	99.2 (97.1 - 101.4)	99.2 (96.8 - 101.7)	97.5 (88.4 - 107.6)	-

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

**ln-transformed values*

The 90% confidence intervals for test/reference ratio of C_{max} and AUC parameters fell entirely within the pre-specified acceptance limits for bioequivalence, 80-125%. It can, thus, be concluded that the test and reference products are bioequivalent.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has not been performed, but an acceptable bridging to a test for a similar product has been made.

The risk/benefit ratio is considered positive and Letrozole Bluefish, 2,5 mg, film-coated tablet is recommended for approval.

Please see below table for the agreed follow-up measures.

Area	Description
Product Information	The applicant commits to submit a variation to the marketing authorization to harmonize SmPC, PL and labeling text to the reference product Femara in accordance with the Commission Decision after the upcoming art. 30 referral.

VI. APPROVAL

The Decentralised procedure for Letrozole Bluefish, 2,5 mg, film-coated tablet was successfully finalised on 27 November 2009.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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