LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Donepezil Bluefish
(donepezil hydrochloride)

SE/H/779/01-02/DC

This module reflects the scientific discussion for the approval of Donepezil Bluefish. The procedure was finalised at 2010-04-14. 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 Donepezil Bluefish 5 and 10 mg film-coated tablets claiming essential similarity to Aricept 5 and 10 mg film-coated tablets marketed in UK by Eisai Ltd. The product contains donepezil hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Aricept 10 mg film-coated tablets marketed by Eisai Ltd in UK.

II. QUALITY ASPECTS

II.1 Introduction

Donepezil Bluefish is presented in the form of film-coated tablets of two strengths containing 5 and 10 mg of donepezil hydrochloride respectively. The excipients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, lactose monohydrate, maize starch, magnesium stearate and Opadry blends (containing hypromellose, macrogol, talc, titanium dioxide and iron oxide yellow). The tablets are packed in HDPE bottles or PVC/Alu blisters.

II.2 Drug Substance

The drug substance donepezil hydrochloride is not described in a Ph. Eur. monograph.

Donepezil hydrochloride is a white to off-white crystalline powder which is soluble in chloroform and water, slightly soluble in ethanol and practically insoluble in ethyl acetate. The structure has been adequately proven and its physico-chemical properties sufficiently described. The donepezil hydrochloride used is a monohydrate and relevant information on polymorphism has been presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance control tests and specifications are adequately drawn up. 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

Donepezil Bluefish film-coated tablets are formulated using excipients described in the current Ph. Eur., except for low-substituted hydroxypropylcellulose and the Opadry coatings. Low-substituted hydroxypropylcellulose complies with NF. All the excipients of the Opadry blends except iron oxide yellow comply with Ph. Eur., and the latter complies with JPE. The only ingredient of animal origin is lactose monohydrate, for which compliance with the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) is certified.

The development and the manufacturing process of the drug product have been sufficiently described.

The product specifications cover appropriate parameters for this dosage form. The analytical methods have been presented. Batch analysis results show that the finished products meet the specifications proposed.

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

Following an oral dose of donepezil, maximal plasma concentrations are reached within 3 to 4 hours. There was no food interaction for the originator product and therefore no restriction with respect to food in the labelling. Donepezil is eliminated as unchanged drug though renal excretion and by metabolism to several metabolites, whereof 6-O-desmetyldonepezil, has similar pharmacological activity as the parent drug. On the basis of in vitro studies, the metabolism of donepezil has been indicated to be mediated by the isoenzymes CYP3A4 and CYP2D6 (to less extent). The terminal half-life is approximately 70 hours, and steady-state is reached within 3 weeks following the start of the therapy. Donepezil displays linear pharmacokinetics.

To support the application, the applicant has submitted as a report one randomized two-period, two-sequence, single dose bioequivalence study of Donepezil Bluefish 10 mg compared with the originator Aricept 10 mg, Eisai Ltd, from the UK market (Study code 125-08). The study was performed in healthy volunteers under fasting conditions. The results are shown below. Based on the submitted bioequivalence study Donepezil Bluefish 10 mg is considered bioequivalent with Aricept 10 mg.

Pharmacokinetic parameters (n=17) Non-transformed values; arithmetic mean ± SD, t_{max} median (range)

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Donepezil Bluefish 10 mg	**500.0 ± 109.0**	**19.2 ± 3.9**	**3.25 (1.50 - 6.00)**
Aricept 10 mg	**497.4 ± 118.6**	**19.1 ± 4.2**	**3.00 (1.50 – 4.50)**
***Ratio (90% CI)**	**100.7 (97.57 – 103.89)**	**99.9 (94.20 – 106.04)**	**na**

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated using ln-transformed values*

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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Donepezil Accord, SE/H/756/01-02/DC. The bridging report submitted by the applicant has been found acceptable.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Donepezil Bluefish, 5 and 10 mg film-coated tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Donepezil Bluefish, 5 and 10 mg film-coated tablets was successfully finalised 2010-04-14.

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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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