LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Olanzapin Bluefish
(olanzapine)

SE/H/950/01-04/DC

This module reflects the scientific discussion for the approval of Olanzapin Bluefish. The procedure was finalised at 2011-03-10. 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 Olanzapin Bluefish, orodispersible tablet, 5, 10, 15 and 20 mg claiming essential similarity to Zyprexa Velotab, orodispersible tablet, 5, 10, 15 and 20 mg marketed in the EU by Lilly Nederland B.V. The product contains olanzapin as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Zyprexa Velotab, 5 mg, orodispersible tablets marketed by Pharmaserve – Lilly in Greece.

II. QUALITY ASPECTS

II.1 Introduction

Olanzapin Bluefish is presented in the form of orodispersible tablets containing 5, 10, 15 or 20 mg of olanzapine. The excipients are calcium carbonate, pregelatinised maize starch, maize starch, lactose monohydrate, crospvidone, aspartame and magnesium stearate. The tablets are packed in peelable aluminium/aluminium blister package.

II.2 Drug Substance

Olanzapine does not have a monograph in the Ph Eur.

Olanzapine is a pale yellow to yellow crystalline powder which is freely soluble in chloroform, soluble in acetone, sparingly soluble in ethyl acetate and insoluble in water. The structure of olanzapine 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

Olanzapin Bluefish orodispersible tablets are formulated using excipients described in the current Ph Eur. 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, polymorphism and stability.

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, when stored in the original package due to sensitivity to moisture.

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 oral administration, olanzapine maximal peak plasma concentrations are reached within 5-8 hours, and the absorption is not affected by food. Olanzapine is metabolised in the liver by conjugative and oxidative (CYP1A2, CYP2D6) pathways. The predominant pharmacological effect comes from the parent compound. The pharmacokinetics of olanzapine are linear and dose-proportional within the approved dose range. The elimination half-life in healthy non-elderly subjects is about 34 hours, however increases depending on age and gender.

To support the application, the applicant has submitted the report of one single dose bioequivalence study of Olanzapin Bluefish 5 mg orodispersible tablets compared with Zyprexa 5 mg orodispersible tablets of Eli Lilly from the Greek market, performed in healthy male subjects under fasting conditions. The given justification for biowaiver for the other three strengths is acceptable.

Regarding the study design, the orodispersible tablets were administered with 240 ml of water after the tablet has disintegrated on the tongue. The general recommendation is administration of orodispersible tablets without water. However, this issue has been discussed before for olanzapine in several other procedures, and it has been concluded by the CHMP that concomitant water intake is unlikely to have any significant influence on the pharmacokinetics for olanzapine orodispersible tablets. The tablets are rapidly disintegrated, and the slow absorption rate indicates that absorption is not determined by disintegration or dissolution of the tablets. Thus, the study design is considered acceptable.

Bioequivalence was properly demonstrated for C_{max} and AUC, and approval is therefore recommended from a clinical point of view.

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 consultation
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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

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 Olanzapin Bluefish, orodispersible tablet, 5, 10, 15 and 20 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Olanzapin Bluefish, orodispersible tablet, 5, 10, 15 and 20 mg was successfully finalised on 2011-03-10.

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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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