LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Olanzapin Sandoz
(SE/H/688/01-06/DC)

(Olanzapine)

This module reflects the scientific discussion for the approval of Olanzapin Sandoz. The procedure was finalised at 2008-01-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sandoz A/S has applied for a marketing authorisation for Olanzapin Sandoz 2.5, 5, 7.5, 10, 15 and 20 mg film-coated tablets claiming essential similarity to Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg coated tablets marketed in the EU by Eli Lilly. The product contains olanzapine as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Zyprexa coated tablets marketed by Eli Lilly in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Olanzapin Sandoz is presented in the form of film-coated tablets containing 2.5, 5, 7.5, 10, 15 or 20 mg of olanzapine. The excipients are lactose monohydrate, hydroxypropylcellulose, microcrystalline cellulose, crospovidone, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide and talc. The 15 mg tablets also contain indigo carmine and the 20 mg tablets also contain red iron oxide. The tablets are packed in Al-blisters or in HDPE containers.

II.2 Drug Substance

Olanzapine does not have a monograph in the Ph Eur.

Olanzapine is a yellowish, crystalline powder which is freely soluble in acetic acid and methylene chloride and slightly soluble in methanol. 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 Sandoz film-coated tablets is formulated using excipients described in the current Ph Eur, except for indigo carmine (15 mg tablets) and red iron oxide (20 mg tablets) 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 polymorphism.

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.

Two impurities of olanzapine have been identified. Based on a subchronic toxicity study, two adequate genotoxicity tests, and literature data, their presence, at the limit of ≤ 0.15 %, is not considered as a toxicological concern.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Olanzapine is well-absorbed, however metabolised with an extensive first pass metabolism. There is a negligible effect of food on the pharmacokinetics of olanzapine (Zyprexa product information). The pharmacokinetics displays linear pharmacokinetics within the approved dosage range (Clinical Pharmacokinetics, Callaghan JT et al 1999). The degree of protein binding is high, approximately 93 % and volume of distribution is 1000 L. The primary metabolic pathways are direct glucuronidation and oxidation mediated by CYP1A2, CYP2D6 (minor) and the flavin-containing monooxigenase system. There are two major inactive metabolites (10-N-glucuronide and 4´N-desmethylolanzapine). Approximately 60 % and 30 % of the dose is excreted renally and via faeces respectively (as metabolites). Clearance ranges somewhere around 12-47 L/h. The elimination half-life is 21-54 hours (mean of 30 hours) (Zyprexa product information).

To support the application, the applicant has submitted two bioequivalence study reports. Study **2005-23-FTA-1** is a three-way randomised single dose cross-over bioequivalence fasting study in healthy male subjects of two 10 mg batches of the test and the 10 mg Zyprexa tablets.

Study **2005-50-FTA-1** is a two-way randomised single dose cross-over bioequivalence fasting study in healthy male subjects of the 15 mg strength of the test and the 15 mg Zyprexa tablets.

Bioequivalence has been shown in both studies versus the originator Zyprexa in terns of rate and extent of absorption.

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 been performed.

The results of the conducted bioequivalence studies 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 Sandoz 2.5, 5, 7.5, 10, 15 and 20 mg film-coated tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Olanzapin Sandoz 2.5, 5, 7.5, 10, 15 and 20 mg film-coated tablets was successfully finalised on 2008-01-16.

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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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