LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Olanzapine Accord
# (olanzapine)

# SE/H/866/01-06/DC

**This module reflects the scientific discussion for the approval of Olanzapine Accord. The procedure was finalised on 28 April 2010. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Accord Healthcare Limited has applied for a marketing authorisation for Olanzapine Accord, film-coated tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg claiming essential similarity to Zyprexa, coated tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg marketed in the EU by Eli Lilly Nederland B.V. 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, 5 mg from the UK market.

# II. QUALITY ASPECTS

## II.1 Introduction

Olanzapine Accord is presented in the form of film-coated tablets containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 20 mg of olanzapine. The excipients are lacots monohydrate, microcrystalline cellulose, crospovidone, hydroxypropylcellulose, magnesium stearate, hypromellose, titanium dioxide, macrogol, polysorbate, iron oxide red (only 20 mg tablet) and indigo carmine aluminium lake (only 15 mg tablet). The tablets are packed in Alu/Alu blister.

## II.2 Drug Substance

There is no monograph in the Ph. Eur on the drug substance Olanzapine for the time being. Olanzapine (form I) is a yellowish crystalline solid which is soluble in n-propanol, sparingly soluble in acetonitrile, slightly soluble in methanol and in dehydrated alcohol and practically insoluble in water. It is known that there are different polymorphic forms of Olanzapine. The polymorphic form I is used for the actual application. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The control tests and specifications for drug substance (Olanzapine Form I) are adequately drawn up. The analytical methods applied are suitably described and validated.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Stability studies are conducted at the storage conditions: Accelerated, intermediate and long term. Up to 48 months results from long term condition are provided.

Based on the data provided, a retest period of 60 months is accepted

## II.3 Medicinal Product

Olanzapine Accord film-coated tablets are formulated using excipients described in the current Ph Eur, except for the colorant indigo carime aluminium lake which is controlled by in-house specifications and Iron oxide red described in the Japanese Pharmacopoeia. Magnesium stearate used in the product is of vegetable origin. Regarding lactose monohydrate 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) has been demonstrated.

The development of the product has been described, the choice of excipients is justified and their functions explained.

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 product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 2 batches of each one of the tablet strengths. The batch analysis results show that the finished products meet the specifications in force at time when analyses were performed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are drawn up.

A shelf-life of 2 years when stored below 30 $^{o}$C is suggested by the applicant. And based on the data provided the suggested shelf-life of 2 years when stored below 30 $^{o}$C is deemed acceptable.

# 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 randomised two-treatment, two-period, two-sequence, single dose bioequivalence study of Olanzapin Accord 5 mg tablets compared with Zyprexa 5 mg tablets of Eli Lilly from the UK market, performed in healthy male subjects under fasting conditions.

The questions raised by CMS on the clinical part on batch size, significant formulation effects and lack of statistical analysis of tmax have all been satisfactorily responded to, see the clinical day 120 report. Long-term stability data has been submitted and is considered acceptable.

Based on the submitted bioequivalence study Olanzapine Accord 5 mg tablets are considered bioequivalent with Zyprexa 5 mg tablets. The results can be extrapolated to other strengths (2.5, 7.5, 10, 15 and 20 mg), according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

### 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 risk/benefit ratio is considered positive and Olanzapine Accord is recommended for approval.

## VI. APPROVAL

The Decentralised procedure for Olanzapine Accord was successfully finalised on 28 April 2010.

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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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