CBG MEB

Public Assessment Report

Scientific discussion

OlaaMeren 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets

(olanzapine)

NL License RVG: 112847, 112851-112855

Date: 5 September 2016

This module reflects the scientific discussion for the approval of OlaaMeren film-coated tablets The marketing authorisation was granted on 10 April 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for OlaaMeren 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets from Meren Pharma B.V.

This medicine is indicated for the treatment of schizophrenia.
Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.
In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder.

Olanzapine is indicated in adults.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg coated tablets (EU License EU/1/96/022) which has been registered through a centralised procedure by Eli Lilly Nederland B.V. since 1996.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each OlaaMeren film-coated tablet contains 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg or olanzapine.

The 2.5 mg tablets are round, biconvex, white film-coated tablets marked with “O” on one side.
The 5 mg tablets are round, biconvex, white film-coated tablets marked with “O1” on one side.
The 7.5 mg tablets are round, biconvex, white film-coated tablets, marked with “O2” on one side.
The 10 mg tablets are round, biconvex, white film-coated tablets marked with “O3” on one side.
The 15 mg tablets are oval, biconvex, light blue film-coated tablets marked with “O” on one side.
The 20 mg tablets are oval, biconvex, light pink film-coated tablets marked with “O” on one side.

The tablets are packed in aluminium/aluminium blister packs and in HDPE containers with LDPE cap.

The excipients in the tablet core are: lactose anhydrous, microcrystalline cellulose, crospovidone and magnesium stearate.

The coating consists of: polyvinyl alcohol, titanium dioxide (E171), talc, lecithin soya (E322), xanthan gum (E415); indigo carmine (E132) (in 15 mg film-coated tablet only) and iron oxide red (E172) (in 20 mg film-coated tablet only).

The 2.5, 5, 7.5 and 10 mg tablets are fully dose proportional. The 15 mg tablet cores have the same composition as the 10 mg tablets with only a higher amount of active substance and the amount of filler was adjusted for compensation. The 20 mg tablet cores are fully dose proportional with the 15 mg product.

II.2 Drug Substance

The active substance is olanzapine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a yellow, crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride and slightly soluble in ethanol. Olanzapine exhibits polymorphism, polymorphic Form I is used. The drug substance does not exhibit isomerism.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The process of the first manufacturer consists of three synthetic steps, and the process of the second ASMF holder consists of two synthetic steps followed by a purification step. No class 1 organic solvents are used in either manufacturing process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification of the MAH is in line with the requirements of the Ph.Eur. monograph on olanzapine and includes additional tests for identification, related substances, residual solvents and particle size distribution. The specification is acceptable. Batch analysis data have been provided on drug substance batches from each supplier demonstrating compliance with the drug substance specification.

Stability of drug substance
Manufacturer I
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). No trends or changes were seen at both storage conditions. The proposed retest period of 18 months and storage condition 'Store in a well closed container at 25°C. Excursions allowed between 15-30°C' are justified.

Manufacturer II
Stability data on the active substance have been provided for at least three full scaled batches stored at the following conditions: 2-8°C (36 months), 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Trends were observed after 18 months at 25°C/60% RH. No trends or changes are seen for the batches stored at 2-8°C. The proposed retest period of 30 months and storage condition 'Store in a refrigerator (2-8°C)' are justified.

II.3 Medicinal Product

Pharmaceutical development
The goal of the development was to make an immediate release tablet essentially similar to the originator product Zyprexa 2.5, 5, 7.5, 10,15 and 20 mg coated tablets. The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concerned the optimization of the formulation and the performance of comparative dissolution studies. A bioequivalence study was performed between the 5 mg strengths of the test and reference product. Comparative *in vitro* dissolution studies (at pH 1.0, pH 4.5 and pH 6.8) have been performed between the 5 mg test and reference batch that were used in the bioequivalence study. The profiles are similar. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are the mixing of the excipients, final blending with addition of magnesium stearate, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches per strength.

Control of excipients
The excipients comply with relevant Ph.Eur. or in-house requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of dosage units, disintegration, assay, related substances, dissolution, microbiological quality and loss on drying. Except for related substances and loss on drying, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on several pilot-scale and production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for either three or four pilot-scaled batches of the 2.5 mg, 10 mg, 15 mg and 20 mg strengths and for three full scaled batches of each strength stored at 25°C/60% RH (36-48 months), 30°C/65% RH (changed to 30°C/75% RH during studies; 36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al-blisters or HDPE bottle packs. A photostability study was performed. The product was demonstrated to be not sensitive to light. The claimed shelf-life of 24 months and storage condition 'Store in the original package in order to protect from moisture' are justified.
In-use stability data for the HDPE bottles have been provided. Two batches of drug product (2.5 mg and 20 mg) were stored for 6 months at 25°C/65% RH in an open 100's count HDPE container. Results of the open can in-use studies sufficiently confirm that no separate in-use shelf-life needs to be defined for the drug product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The lactose anhydrous used in the product is of animal origin, but is collected from milk for human consumption in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products. A theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that OlaaMeren film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since OlaaMeren is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zyprexa, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Olanzapine is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product OlaaMeren 5 mg (Meren Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Zyprexa 5 mg tablets (Eli Lilly Nederland B.V., the Netherlands).

The choice of the reference product in the bioequivalence study is justified, as Zyprexa is registered via the centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The MAH did not use the highest strength in the bioequivalence study. Given the existing knowledge on anti-psychotics, the use of the lower strength is justified for safety reasons.

Biowaiver
A biowaiver for the 2.5 mg, 7.5 mg, 10 mg and 20 mg strengths has been granted. The different strengths are manufactured by the same manufacturer and process. The drug input has been shown to be linear over the therapeutic dose range and dissolution profiles have been compared.
The results of the bioequivalence study with the 5 mg can be extrapolated to the higher strengths.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy subjects (17 males/9 females), aged 21-45 years. Each subject received a single dose (5 mg) of one of the 2 olanzapine formulations. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.50, 0.75, 1.25, 2, 3, 4, 5, 6, 7, 8, 10, 14, 24, 48, 72, 96, 120 and 144 hours after administration of the products.

The study design is acceptable and in accordance to the Guideline on the Investigation of Bioequivalence. Food does not affect the absorption of olanzapine. Hence a study under fasting condition is appropriate as it is considered to be the most sensitive to detect a potential difference between formulations.
Based on the known half-life of olanzapine (32-37 hours), the wash-out period of 21 days is in accordance to the BE guideline recommendation of ≥ 5x half-lives to prevent carry-over effects.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 26 subjects completed the study but only 24 subjects were included for pharmacokinetic analysis as the other 2 were alternates according to the protocol.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olanzapine under fasted conditions.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	255 ± 72	274 ± 81	6.4 ± 1.7	5.4 (2 – 10)	--
Reference	249 ± 71	268 ± 136	6.3 ± 1.7	5.7 (2 – 8)	--
***Ratio (90% CI)**	1.02 (0.98 – 1.07)	1.02 (0.98 – 1.06)	1.02 (0.97 – 1.07)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The MAH also provided the statistical analysis of all 26 subjects, i.e. including the two alternates; the 90% confidence intervals were within the acceptance range.
Based on the submitted bioequivalence study OlaaMeren 5 mg is considered bioequivalent with Zyprexa 5 mg tablets.

Safety
Seven subjects with test product and 9 subjects with the reference product experienced at least 1 mild to moderate adverse event (e.g. dizziness, nausea, headache, insomnia, tiredness, back pain).

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to OlaaMeren.

- Summary table of safety concerns as approved in RMP

Important identified risks	Weight Gain Glucose Dysregulation Dyslipidaemia
Important potential risks	Cardiac death (presumed sudden cardiac death)
Missing information	-

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zyprexa. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic

profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

OlaaMeren 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zyprexa coated tablets. Zyprexa is a well-known medicinal product with an established favourable efficacy and safety profile

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for OlaaMeren film-coated tablets with the reference product, and have therefore granted a marketing authorisation. OlaaMeren 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets was authorised in the Netherlands on 10 April 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Minor change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product.	IA	1-12-2014	31-12-2014	Approval	No
Change in batch release site.	IA	11-2-2015	26-3-2015	Approval	No
Transfer MAH, change in product name.	MA transfer	29-2-2016	18-3-2016	Approval	No
Change to an importer, batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for importation and/or batch release not including batch control/testing.	IA/G	26-5-2016	13-6-2016	Approval	No