CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Olanzapine Jubilant 2.5, 5, 7.5, 10, 15 and 20 mg, film-coated tablets Jubilant Pharmaceuticals N.V., Belgium

olanzapine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1659/001-006/DC
Registration number in the Netherlands: RVG 104371-104376

30 August 2010

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines, thiazepines, and oxepines
ATC code:	N05AH03
Route of administration:	oral
Therapeutic indication:	schizophrenia; maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response; moderate to severe manic episode; prevention of recurrence in patients with bipolar disorder in patients whose manic episode has responded to olanzapine treatment
Prescription status:	prescription only
Date of authorisation in NL:	24 March 2010
Concerned Member States:	Decentralised procedure with UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Olanzapine Jubilant 2.5, 5, 7.5, 10, 15 and 20 mg, film-coated tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 24 March 2010 in the Netherlands.

The product is indicated for:

- treatment of schizophrenia.
- maintenance of clinical improvement during continuation therapy in patients who have shown an initial treatment response.
- treatment of moderate to severe manic episodes.
- prevention of recurrence in patients with bipolar disorder in patients whose manic episode has responded to olanzapine treatment .

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

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems. Olanzapine is a member of the so-called atypical antipsychotics, as opposed to the classical antipsychotics, such as haloperidol, showing greater affinity to Serotonin 5HT2A-receptors than to Dopamine D2-receptors. Atypical antipsychotics would elicit fewer extra pyramidal symptoms and would have an effect on the negative symptoms of the disease.
In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5-HT2A/2C, 5-HT3, 5-HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors m1-m5; α-1 adrenergic; and histamine H1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in-vitro affinity for serotonin 5-HT2 than dopamine D2 receptors and greater 5-HT2 than D2 activity in vivo, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

The efficacy and safety of olanzapine has been demonstrated in randomised, placebo-controlled and comparative trials in positive and negative symptoms of schizophrenia, and also as monotherapy or in combination with mood stabilizers in the treatment of acute manic or mixed episodes associated with bipolar disorder. A summary of these studies may be found in the EPAR of Zyprexa to be found on website of the EMA (http://www.ema.europa.eu/humandocs/PDFs/EPAR/Zyprexav/316299en6.pdf).

This decentralised 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/1/96/022) which have been registered through a centralised procedure by Eli Lilly since 27 September 1996.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the 10 mg product is compared with the pharmacokinetic profile of the reference product Zyprexa 10 mg coated tablets, registered in Europe. A bioequivalence study is the widely accepted means of demonstrating that difference of use of

different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is olanzapine, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. However, a monograph on olanzapine is recently published in the Pharmeuropa (vol 20. No. 4, October 2008, 705-708). The drug substance is a yellow crystalline powder. It is practically insoluble in water, freely soluble in methylene chloride, slightly soluble in methanol and in ethanol. Olanzapine is known to exist in different polymorphic forms which can be distinguished by X-ray powder diffraction pattern. Olanzapine used in this product is form I. Olanzapine does not have any chiral center

The Active Substance Master File (ASMF) procedure is used for 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 synthesis processes, starting materials, solvents and reagents have been included in the description. The drug is synthesized in a five step process. The manufacturing process has been adequately described. The active substance has been adequately characterized. The specification for the starting materials is acceptable. No class I solvents are used in the manufacturing process.

Quality control of drug substance
The drug substance specifications have been established using in-house and Ph.Eur. methods. Stability indicating properties of the in house method for assay and related substances have been shown. The specification is acceptable in view of the route of synthesis and the various European guidelines. It has been brought in line with the published draft monograph on olanzapine. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches. The MAH committed to cross-validate the in-house HPLC method for related substances and the assay with the methods of Ph.Eur. monograph on olanzapine once published.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (24 months) and at 40°C/75% RH (6 months). The batches were stored in the commercial packaging. Results remained within the limits and no other specific trends were noted. The claimed retest

period of 24 months could therefore be granted. The proposed storage condition is not required, however accepted.

**Ph.Eur.is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
All Olanzapine Jubilant film-coated tablets are off-white to pale yellow tablets debossed with "J" on one side; the other side is debossed with the strength, *i.e.* "2.5", "5", "7.5", "10", "15" or "20".

The film-coated tablets are packed in cold-formed aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, hydroxypropylcellulose (E463), crospovidone (E1202), microcrystalline cellulose (E460), magnesium stearate (E572).
Tablet coat - polyvinyl alcohol, titanium dioxide (E171), talc (E553b), lactose monohydrate, triacetin.

The 2.5 mg, 5 mg, 7.5 mg, 10 mg core tablets are dose proportional. The 15 mg and 20 mg have the same composition as the 10 mg product except for the amount of active substance which is compensated by the amount of lactose monohydrate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim was to create a film-coated tablet which could be considered bioequivalent to innovator product Zyprexa. The choices of the packaging and manufacturing process are justified. Comparative dissolution profiles were provided of the 10 mg test and reference products used in the bioequivalence studies. Thee dissolution profiles of the tablets are comparable; over 85% is dissolved in 15 minutes. Also, comparative dissolution profiles of all strengths of test and reference were provided. The test and reference products used in the bioequivalence studies are acceptable from chemical point of view.

Manufacturing process
The tablets are manufactured by means of a 12 step process. The intragranular material and the binder are granulated. The extragranular material is then added to the granules, followed by compression, coating and packing of the tablets. The manufacturing process has been adequately validated according to relevant European guidelines, the conditions at which the common blend, compressed and coated tablets can be stored should be clarified. Process validation data on the product has been presented three pilot-scale batches of each strength. The product is manufactured using conventional manufacturing techniques and is considered to be a standard process.

Control of excipients
The excipients comply with the specifications of the Ph.Eur except for the Opadry® coating material. For the Opadry® coating material an internal specification by the supplier is given. The substances used in the Opadry coating are listed in the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of olanzapine and opadry colour, average mass, water, disintegration time, uniformity of dosage units (content uniformity), dissolution test, related substances, assay, and microbiological quality. Release and end of shelf-life specification are identical; the set limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical on two batches of each strength have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on two pilot-scale batches of the each strength stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The batches were stored in aluminium-aluminium cold form blisters. The simulate bulk pack bulk pack was stored at 25°C/60%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Results for all parameters stayed within the limits, no specific patterns are noted. A photostability study was carried out, demonstrating that the product is not sensitive to light.
The claimed shelf-life of 24 months for the commercial packing and the claimed storage condition of 'This medicinal product does not require any special storage conditions' are justified. The claimed holding time of 6 months for the bulk pack is justified, a storage condition 'store below 25°C' is applicable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate and magnesium stearate are of bovine origin. It is declared that the milk used in lactose monohydrate and lactose anhydrous is sourced from healthy animals and collected under the same conditions as milk for human consumption. For magnesium stearate a statement on minimizing the risk of TSE was provided.

II.2 Non clinical aspects

This product is a generic formulation of Zyprexa, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of olanzapine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Olanzapine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Olanzapine Jubilant 10 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Zyprexa 10 mg coated tablets (Eli Lilly, the Netherlands).

The choice of the reference product
Zyprexa coated tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Design
A single-dose, open-label, balanced, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects (including 4 standby subjects and 2 extra subjects), with a mean age of 30.7 years. Each subject received a single dose (10 mg) of one of the 2 olanzapine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. The subjects were remained in supine position for the first 4 hours after dose administration. They were instructed to refrain from drinking water from 1 hour before until 2 hours after dosing in each period. There were 2 dosing periods, separated by a washout period of 23 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 10, 12, 16, 24, 48, 72, 96 and 144 hours after administration of the products.

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.

Olanzapine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of olanzapine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results
Forty subjects were dosed. There were 4 dropouts in the study. Two subjects withdrew their informed consent prior to period II. One subject was withdrawn due to the protocol deviations prior to period II and antoher subject was withdrawn prior to period II due to emesis. Thirty-six subjects completed both the periods and were included in pharmacokinetic and statistical analyses.

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

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	523.46 ± 131.15	557.62 ± 143.05	13.49 ± 3.28	3.75 (1.00-10.00)	33.66 ± 5.50
Reference	524.24 ± 118.94	559.86 ± 136.38	12.99 ± 3.36	6.00 (2.00-10.00)	34.51 ± 6.20
***Ratio (90% CI)**	1.00 (0.96-1.03)	1.00 (0.96-1.03)	1.04 (0.99-1.09)	--	--
CV (%)	8.6	8.8	12.0	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of olanzapine under fasted conditions, it can be concluded that Olanzapine Jubilant 10 mg and Zyprexa 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The MAH sufficiently justified performing the bioequivalence study with the 10 mg tablet. Plasma concentrations of olanzapine after single doses are linear and doseproportional within the approved dosage range (5 to 20 mg). The ratio between the amounts of excipients is similar, and the dissolution of the biobatch and additional strengths is fast. All requirements for a biowaiver stated in the NfG on Investigation of Bioavailability and Bioequivalence have been fulfilled. The results from the bioequivalence study can therefore be extrapolated to the other strengths.

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).

Risk management plan

Olanzapine was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of olanzapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zyprexa.

Readability test

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. A total number of 21 questions were asked. Eighteen questions specifically addressed the key safety messages of the leaflet in a randomized order; the other 3 questions were meant to obtain a general impression of the package leaflet, including aspects as design and lay-out.

The 18 questions specifically addressing the key aspects of the package leaflet did not reveal any weaknesses. Nevertheless some changes were introduced in the PIL after the first round, based on the participants' feedback on the open questions. Serious side effects that require the patient to contact their doctor were moved to the start of section 4, a reference to section 4 was added in section 2, and the advise to contact a doctor in case any of the (other) listed side effects becomes serious, was more pronounced (amongst others by using a bold font). Fewer remarks regarding section 4 of the PL were obtained in the subsequent test-round.

The results of the user testing are acceptable according to the guideline on the readability,as '90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it and act upon it'.

The results show that the leaflet is easy to read and understandable. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Olanzapine Jubilant 2.5, 5, 7.5, 10, 15 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other olanzapine containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Olanzapine Jubilant 2.5, 5, 7.5, 10, 15 and 20 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 January 2010. Olanzapine Jubilant 2.5, 5, 7.5, 10, 15 and 20 mg, film-coated tablets were authorised in the Netherlands on 24 March 2010.

A European harmonised birth date has been allocated and subsequently the first data lock point for olanzapine is 31 March 2010. The first PSUR will cover the period to March 2010, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 30 November 2014.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH committed to cross-validate the in-house HPLC method for related substances and the assay with the methods of Ph.Eur. monograph on olanzapine once published.

Quality - medicinal product

- The MAH committed to perform process validation on the first three consecutive commercial batches of each strength.
- The MAH committed to analyse the first three commercial batches as per proposed finished product specification and method of analysis.
- The MAH committed that stability studies will be performed on three industrial-size batches covering the whole proposed shelf-life.
- The MAH committed that all the commercial supplies in the bulk pack will be shipped under controlled conditions.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached