CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Olanzapine Jubilant 5 mg, 10 mg, 15 mg and 20 mg, orodispersible 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/1717/001-004/DC
Registration number in the Netherlands: RVG 105166, 105168-105170

15 June 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:	28 April 2010
Concerned Member States:	Decentralised procedure with BE
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 5 mg, 10 mg, 15 mg and 20 mg, orodispersible tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 28 April 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 Velotab 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets (EU/1/99/125) which have been registered through a centralised procedure by Eli Lilly since 3 February 2000.

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 product is compared with the pharmacokinetic profile of the reference product Zyprexa Velotab 5 mg, 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.

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/EMEA 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 orodispersible tablets are yellow, round, flat face beveled edge tablets with a characteristic flavor which are placed in the mouth or alternatively dispersed in water.

Olanzapine Jubilant 5 mg is debossed with “D5” on one side and “CO” on the other side of the tablet.
Olanzapine Jubilant 10 mg is debossed with “D10” on one side and “CO” on the other side of the tablet.
Olanzapine Jubilant 15 mg is debossed with “D15” on one side and “CO” on the other side of the tablet.
Olanzapine Jubilant 20 mg is debossed with “D20” on one side and “CO” on the other side of the tablet.

The excipients are: mannitol (E421), aspartame (E951), hydroxypropylcellulose (E463), strawberry flavor, colloidal anhydrous silica (E551), magnesium stearate (E470b).

The different strengths are dose proportional.

The orodispersible tablets are packed in aluminium blisters.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to create a orodispersible tablet which could be considered bioequivalent to innovator product Zyprexa Velotab. The dissolution of all strengths is fast in all mediums tested. The comparative dissolution data of the tablets showed that the batches exhibit dissolution profiles which are similar to the respective reference products and to the biobatch revealing more than 85% in 15 minutes of dissolution. The choice of the manufacturing process is justified. The test and reference products used in the bioequivalence studies are acceptable from a chemical point of view.

Manufacturing process
The tablets are manufactured by means of a five step process. The product is manufactured using conventional manufacturing techniques and is considered to be a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented on two pilot-scale batches of each strength.

Control of excipients
Except for strawberry flavor and hydroxypropylcellulose, Ph.Eur. and USP methods are used. For strawberry flavor an in-house specification was provided. These specifications are acceptable.

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

Stability of drug product
Stability data on the product has been provided for two pilot scaled batches of each strength stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The batches were stored in aluminium blisters. The simulate bulk pack was stored at 25°C/60%RH. The conditions used in the stability studies are according to the ICH stability guideline. Except for slight increases in two impurities, no specific trends were observed for any of the tested parameters at both storage conditions. The claimed shelf life of 24

months was granted. No special storage conditions are required. The MAH committed to perform a stability study up to 24 months on the first three production batches of all strengths.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
All the excipients used are of vegetable or mineral origin except magnesium stearate. It is confirmed that the manufacture of magnesium stearate is in compliance with the GMP 'Guideline Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products'. A TSE statement was provided.

II.2 Non clinical aspects

This product is a generic formulation of Zyprexa Velotab, 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 5 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Zyprexa Velotab 5 mg orodispersible tablets (Eli Lilly, the Netherlands).

The choice of the reference product
Zyprexa Velotab orodispersible 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, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19-41 years. Each subject received a single dose (5 mg) of one of the 2 olanzapine formulations after an overnight fast. Just before administration, 20 ml of water was administered to the volunteers and the volunteer were asked to swirl the water in mouth to moisten the buccal cavity. The tablets were placed on the subjects tongue. The volunteers were then asked to swirl the tablet around the tongue and upper palette for 60 sec or until it disintegrates. After complete disintegration, the contents were swallowed with saliva. Subjects were restricted from drinking water at least 1 h before dosing and 2 h after dosing (except for the 20 ml to moisten the buccal cavity). Fasting was continued for 4 hrs after dosing. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 18, 24, 48, 72, 96, 120 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
One subject dropped out and eight subjects were withdrawn. Seven subjects were withdrawn from the study due to adverse events and one subject was withdrawn due to non-compliance with the protocol. Twenty-three subjects completed the study entirely and were included in the analysis.

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

Treatment N=23	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	234.82 ± 113.57	253.99 ± 116.78	8.8721 ± 3.90381	5.5	-
Reference	224.64 ± 113.37	232.47 ± 113.75	9.1220 ± 3.53091	5.0	-
***Ratio (90% CI)**	1.06 (0.98-1.14)	1.11 (1.02-1.20)	0.95 (0.87-1.04)	-	-
CV (%)	16.7	14.9	16.3	-	-

$AUC_{0-\infty}$ 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 5 mg and Zyprexa Velotab 5 mg orodispersible 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 10, 15 and 20 mg orodispersible tablets are dose proportional with the 5 mg tablet. The tablets have been manufactured by the same manufacturing process by the same manufacturer. In addition, olanzapine shows linear pharmacokinetics. The results of the bioequivalence study performed with the 5 mg film-coated tablets therefore apply 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

Readability test

The MAH submitted a bridging document to extrapolate the readability testing results of the Olanzapine Jubilant film-coated tablets (parent PIL) to the Olanzapine Jubilant orodispersible tablets (daughter PIL). The lay-out, size and style have been compared between these PILs as well as a detailed content comparison. There are no significant differences between the parent and daughter PILs. Therefore, the readability testing results are applicable to the proposed PIL.

Readability of the package leaflet has sufficiently been demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Olanzapine Jubilant 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Zyprexa Velotab orodispersible tablets. Zyprexa Velotab 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 state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Olanzapine Jubilant 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets with the reference product, and has therefore granted a marketing authorisation. The decentralised procedure was finished on 13 February 2010. Olanzapine Jubilant 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets were authorised in the Netherlands on 28 April 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 a stability study on the first three production batches of all strengths, in the marketed container/closure system (long-term stability study for the duration of the proposed shelf life and accelerated condition for a period of six months, according to the set protocol).
- The MAH committed to provide the updated stability data for the complete 24 months shelf-life when out of specifications occur or on request.

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
Change in the address of the active substance manufacturer and increase in the batch size of the active substance	NL/H/xxxx/ IA/0017/G	A.4 & B.I.a.3.a	Not started yet			
PSUR	Not applicable	PSUR	Not started yet			