CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Olanzapine Ranbaxy 2.5/5/7.5/10/15/20 mg tablets Ranbaxy Belgium B.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/1425/001- 006/DC
NL license RVG: 102843,102845, 102849,102850,102851,102852

20 July 2010

Pharmacotherapeutic group:	antipsychotics; diazepines, oxazepines, thiazepines and oxepines
ATC code:	N05AH03
Route of administration:	oral
Therapeutic indication:	schizophrenia; moderate to severe manic episode; 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:	9 July 2010
Concerned Member States:	Decentralised procedure with AT, CZ, DE, DK, DK, FI, FR, HU, IS, PT, SE, SK, (all strenghts); IE (not for 20 mg); BE, ES (not for 15 mg and 20 mg); PL, RO (not for 2.5 and 7.5 mg); IT (only 2.5 mg, 5 mg, and 10 mg), and BG (only 2.5 mg, 5 mg, 7.5 mg, and 10 mg)
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 Ranbaxy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets, from Ranbaxy Belgium B.V. The date of authorisation was on 9 July 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 $5HT_{2A}$-receptors than to Dopamine D_2-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; <100nM) for serotonin $5HT_{2A/2C}$, $5HT_3$, $5HT_6$; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; $alpha_1$ adrenergic; and histamine H_1 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 $5HT_2$ than dopamine D_2 receptors and greater $5HT_2$ than D_2 activity in *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/olanzapine_mylan/H-961-en6.pdf).

This decentralised procedure concerns a generic application claiming essential similarity with Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg coated tablets (EU License EU/1/96/022) which have been registered through a centralised procedure by Eli Lilly since 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Zyprexa 5 mg tablets, registered in the Netherlands. 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. This generic product can be used instead of its reference product.

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, and 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 this product type 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. The active substance is practically insoluble in water, freely soluble in methylene chloride, slightly soluble in methanol and sparingly soluble in Acetonitrile. 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 and does not exhibit isomerism.

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.

Manufacture
A brief description and flow chart of the manufacturing process was provided. Olanzapine is manufactured in three steps which have been sufficiently described. The active substance is adequately characterised.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines.
In addition, the proposed limits for triethylamine and N-Methyl piperazine are adequately qualified.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 2-8ºC (12 months) and at 25ºC/60%RH (6 months). The batches were adequately stored. No clear changes were seen in the stability study at both storage conditions. The storage conditions used are adequately justified. The proposed re-test period of 12 months and storage condition are acceptable.

Medicinal Product

Composition
The products are formulated as tablets which are packaged in cold form blister packs of OPA-Al-PVC/Al.

Olanzapine Ranbaxy 2.5 mg are light yellow to yellow coloured, round, biconvex tablets, debossed with '*O4*' on one side and plain on the other side.
Olanzapine Ranbaxy 5 mg are light yellow to yellow coloured, round, biconvex tablets, debossed with '*O5*' on one side and plain on the other side.
Olanzapine Ranbaxy 7.5 mg are light yellow to yellow coloured, round, biconvex tablets, debossed with '*O6*' on one side and plain on the other side.
Olanzapine Ranbaxy 10 mg are light yellow to yellow coloured, round, biconvex tablets, debossed with '*O7*' on one side and plain on the other side.
Olanzapine Ranbaxy 15 mg are light yellow to yellow coloured, round, biconvex tablets, debossed with '*O8*' on one side and plain on the other side.
Olanzapine Ranbaxy 20mg are light yellow to yellow coloured, round, biconvex tablets, debossed with '*O9*' on one side and plain on the other side.

The excipients are: lactose anhydrous, microcrystalline cellulose, low substituted hydroxypropyl cellulose And magnesium stearate.

The excipients and packaging are usual for this type of dosage form. The contents of the six tablet formulations are dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of this development was to seek essential similarity with the innovator product. The composition, *in-vitro* and *in-vivo* studies and the impurity profile have been compared. The composition of the tablets used in the bio-equivalence study is similar to the composition of the batches proposed for marketing. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The tablets are produced by direct compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches per tablet strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scaled batches will be performed post authorisation.

Excipients
The excipients comply with the Ph. Eur. or US-NF*. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, uniformity of dosage units, water content, dissolution, assay, related substances and microbial limits.
The proposed specification is acceptable. The shelf-life limits for water content, dissolution and related substances differ from the proposed release specification.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site has been provided on two pilot-scale batches per tablet strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two batches per tablet strength stored at 25ºC/60%RH (12 months), 40ºC/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu-oPA/Alu/PVD-blister or in simulated bulk pack (only stored at 25ºC/60%RH). The amount of desiccant used in the stability study is proportional to the amount used in the commercial size bulk packaging.

During the stability testing, both at accelerated and long-term conditions, a slight increase in water content, any unknown and total impurities and some variability in assay can be observed. All results remain well within limits.
The proposed shelf-life, 24 months, and the proposed storage condition '*no additional storage condition*' are acceptable based on the submitted stability data.
The MAH has committed to continue long term stability studies in the blister packaging continued to 36 months. In addition the MAH has committed to perform long term stability studies on the first three production scale batches.
The MAH will also continue determining polymorphic form 'form II' content in the drug product over the entire proposed shelf-life and will include this test in the drug product specification on the agency's request. The information regarding this impurity obtained during the stability studies will be submitted as soon as these are available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

** Ph.Eur. and US-NF, are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively. (NF stands for National Formulary).*

II.2 Non clinical aspects

These products are generic formulations of Zyprexa coated tablets, which are 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 products are intended as a substitute for other identical products on the market. The approval of these products 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 one bioequivalence study in which the pharmacokinetic profile of the test product Olanzapine Ranbaxy 5 mg tablets (Ranbaxy Belgium B.V., Belgium) is compared with the pharmacokinetic profile of the reference product Zyprexa 5 mg film-coated tablets (Eli Lilly, the Netherlands).

The choice of the reference product
Zyprexa 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 batch is identical to the formula proposed for marketing.

Study design
An open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study was carried out under fasted conditions in 44 healthy Caucasian male volunteers, aged 19-32 years. Each subject received a single dose (5 mg) of one of the 2 olanzapine formulations. The tablet was orally administered with 240 ml water after an overnight fasting period of at least 10 hours. No food was allowed till 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected predose and at 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0, 144.0 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.
It was noted however that the long term stability data of the analyte in plasma covers the storage period of 42 days, while the subjects' plasma samples were stored for 49 days. Also, it was not known under what temperature the long term stability study had been conducted. The MAH provided the member states with the requested data and therefore this concern is considered resolved.

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 completed the study. One subject was withdrawn due to an adverse event (preauricular adenopathy due to toxoplasmosis) and three other subjects dropped out of the study due to changes in personal schedule.
Pharmacokinetis and statistical analysis was performed on data from 40 subjects who completed both study periods.

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

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	228.53 ± 79.87	245.54 ± 80.09	7.72 ± 2.47	3.5 (1.0 – 7.0)	35.27 ± 7.05
Reference	228.23 ± 70.15	244.15 ± 75.45	7.80 ± 2.07	3.99 (2.0 – 10.0)	34.80 ± 6.51
***Ratio (90% CI)**	0.98 (0.92 – 1.04)	0.99 (0.93 – 1.05)	0.97 (0.90-1.05)	---	---
CV (%)	16.1	15.3	21.4	---	---

$AUC_{0-\infty}$ 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 Ranbaxy 5 mg tablets and Zyprexa 5 mg film-coated 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
A biowaiver could be granted, as the following requirements were met:
- the pharmaceutical products are manufactured by the same manufacturer and process.
- the pharmacokinetics of olanzapine has been shown to be linear over the therapeutic range.
- all tablet strenghths are dose proportional.

- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch.

Therefore the results of the bioequivalence study with the 5 mg strength also apply to the 2.5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets.

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 proposed PLs should be identical to the harmonized PL for Zyprexa and Zyprexa Velotab, except for product specific information. The MAH adequately adapted the PLs in accordance with the comments submitted by the Member States. At the end of the procedure the text was identical to the published texts of Zyprexa and Zyprexa Velotab published on the EMEA website.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Olanzapine Ranbaxy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg 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 MAH committed to provide an updated Pharmacovigilance system within three months after obtaining the marketing authorisation.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates. Texts are identical to the published texts of Zyprexa and Zyprexa Velotab published on the EMEA website.

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 Ranbaxy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 June 2009. Olanzapine Ranbaxy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg tablets are authorised in the Netherlands on 9 July 2010.

A European harmonised birth date has been allocated. The first PSUR will cover the period from June 2009 to June 2010, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 28 June 2014.

The following post-approval commitment was made during the procedure:

<u>Quality – medicinal product</u>

- The has committed to validate the first three commercial scale batches of each strength.
- The MAH has committed to continue long term stability studies in the blister packaging continued to 36 months. In addition the MAH has committed to perform long term stability studies on the first three production scale batches.
- The MAH will continue determining polymorphic form ‘form II’ content in the drug product over the entire proposed shelf-life and will include this test in the drug product specification on the agency’s request. The information regarding this impurity obtained during the stability studies will be submitted as soon as these are available.

<u>Pharmacovigilance</u>

- The MAH committed to provide an updated Pharmacovigilance system within three months after obtaining the marketing authorisation. The Pharmacovigilance system should be updated as follows:
  - The general description of the arrangements with the contractual partners and the statements with the contractual partners should be embedded in the Pharmacovigilance system. If the MAH ensures that there are no general arrangements with contractual partners regarding Pharmacovigilance, a product specific addendum is accepted.
  - A brief description of the auditing of sub-contractors in general, non-product specific, should be present in the updated Pharmacovigilance system.

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
1) Implementation of change(s) requested by the EMEA/ National Competent Authority following the assessment of a class labelling, or amendments to reflect a competent authority Core SPC; Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH. 2) Adaptation to CHMP/PhVWP decisions on Antipsychotics 2008-2009 - PhVWP decisions of July and September 2009 and BfArM-Anhörung nach dem Stufenplan (75.02-3822-V12369/82400/09).	NL/H/1425/ 001-006/W S/001/G	WS	26-3-2010	16-4-2010	Approved	N