European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT
FOR
Olanzapine Glenmark

International Nonproprietary Name: **olanzapine**

Procedure No. EMEA/H/C/1085

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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TABLE OF CONTENTS

Page

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Glenmark Generics (Europe) Ltd. submitted on 28 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Olanzapine Glenmark, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg film-coated tablets
- Marketing authorisation holder: Eli Lilly Nederlands B.V.
- Date of authorisation: 27-09-1996
- Marketing authorisation granted by:
    - Community
- (Community) Marketing authorisation number: EU/1/96/022/002-019-023-029-004-020-024-030-011-006-025-031-008-009-010-026-032-012-021-027-033-014-022-028-034

■ *Medicinal product authorised in the Community/Member State where the application is made or European reference medicinal product:*

- Product name, strength, pharmaceutical form: Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg film-coated tablets
- Marketing authorisation holder: Eli Lilly Nederlands B.V.
- Date of authorisation: 27-09-1996
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■ *Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:*

- Product name, strength(s), pharmaceutical form(s): Zyprexa 10 mg film-coated tablets
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 27-09-1996
- Marketing authorisation granted by:
    - Community
- Marketing authorisation number: EU/1/96/022/008-009-010-026-032
- Bioavailability study reference number/EudraCT number(s): 60679

- Product name, strength, pharmaceutical form: Zyprexa Velotab 10 mg orodispersible tablets
- Marketing authorisation holder: Eli Lilly Nederlands B.V.
- Date of authorisation: 03-02-2000
- Marketing authorisation granted by:
    - Community
- Marketing authorisation numbers: EU/1/99/125/002, 006, 010, 014
- Bioavailability study reference number/EudraCT number(s): 60679

The Rapporteur appointed by the CHMP was Pierre Demolis.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 28 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2009.
- During the meeting on 16-19 March 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant The final list of outstanding issues was sent to the applicant on 23 July 2009.
- The applicant submitted the responses to the CHMP list of outstanding issues on 21 August 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 September 2009.
- During the meeting on 21-24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Olanzapine Glenmark on 24 September 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 September 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on xx-xx-2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Olanzapine Glenmark 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets is a generic medicinal product containing olanzapine as active substance.

The reference medicinal products are Zyprexa and Zyprexa Velotab which contain olanzapine.

Olanzapine, a thienobenzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. As atypical antipsychotics are generally classified those drugs, which in contrast to classical antipsychotics (e.g. haloperidol), have greater affinity for serotonin 5-HT_2 receptors than for dopamine D_2 receptors and cause fewer extrapyramidal symptoms (EPS).

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.

The indication proposed for Olanzapine Glenmark is the same as authorized for the reference medicinal product Zyprexa.

2.2 Quality aspects

Introduction

Olanzapine Glenmark is presented in the form of tablets. The tablets contain 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg of olanzapine as active substance. Other ingredients are defined in the SPC section 6.1.

It is packaged into blisters made of Al/Al.

Active Substance

The chemical name of olanzapine is: (2-methyl-4-(4-methyl-1-piperazinyl)-10h-thieno[2 ,3-b] [1,5] benzodiazepine, corresponding to the molecular formula $C_{17}H_{20}N_4S$ and relative molecular mass 312.44. It is pale yellow to yellow crystalline odourless powder, practically insoluble in water, freely soluble in chloroform, soluble in dichloromethane and very slightly soluble in methanol. Solubility in aqueous media decreases with increasing of pH. Olanzapine exists in many polymorphic forms; polymorph I is consistently manufactured by the current synthesis.

- Manufacture

The manufacturing of olanzapine consists of five synthetic steps leading to Olanzapine Form-I. An ASMF has been submitted. Critical process parameters of all stages with appropriate justification have been described. Starting materials are described in sufficient detail as well as synthetic intermediates.

- Specification

The drug substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (IR), solubility (Ph.Eur.), loss on drying (Ph.Eur.), residue on ignition (Ph.Eur.), heavy metals (Ph.Eur), assay (HPLC), related substances (HPLC), residual solvents (GC) and particle size (laser diffraction).
Analytical results were provided for three batches. All results complied with specifications claimed.

- Stability

The stability studies have been carried out on three batches of active substance in long-term (25°C/60 % RH) and in accelerated conditions (40°C/75% RH). The stability samples have been stored in a mini-size simulation of the original packaging.
Forced degradation studies with Olanzapine are performed by treatment with heat, under acidic and alkaline conditions, under oxidizing conditions, humidity as well as under light stress conditions.
The active substance remained stable and within the specifications throughout the proposed re-test period in long term conditions and up to three months in accelerated conditions. The content of unidentified impurity exceeds the specification NMT 0.10%. In all case, the total impurities remain under the limit (NMT 0.50%). Results demonstrated that polymorphic form I remains unchanged throughout the proposed re-test period. All others parameters are well within the specification limit under both accelerated and long term conditions.
Based on the provided stability data the claimed re-test period and storage conditions can be accepted.

Medicinal Product

- Pharmaceutical Development

The overall target was to produce a tablet bioequivalent to the reference medicinal product Zyprexa 10 mg film-coated tablets and Zyprexa Velotabs 10 mg orodispersible tablets.
The formulation development was initiated taking into account potential stability problems seen in other benzodiazepines, the solubility of the active substance and the low strength of the finished product.
The drug substance is known to be sensitive to moisture. For this reason, a simple mixing direct compression process was selected.
Olanzapine is practically insoluble in water, however it has been demonstrated by appropriate solubility studies that olanzapine even in the 20 mg tablets - highest strength - was completely soluble in 250 ml of a range of media.
The existence of different polymorphic forms has been demonstrated for olanzapine. The drug substance manufacturer form is form I, as characterised by XRD. Active substance particle size is controlled by appropriate specification.
The excipients used Olanzapine Glenmark tablets are well known and widely used for the manufacture of solid dosage forms. Appropriate drug substance - excipient compatibility studies have been carried out with different excipients in order to screen suitable ones. No significant change was observed in the impurity levels during these studies.
A comparative study of impurities profiles has been performed for 2.5 mg, 5 mg and 10 mg strengths between 1 pilot batch of generic product and one batch of reference product Zyprexa tablet. For the 5 mg and 10 mg strengths one batch of reference product Zyprexa Velotab has also been compared.
No significant difference is observed for immediate release tablet between the generic and the reference product Zyprexa tablet whereas the level of impurities in Zyprexa Velotab was found slightly higher.

- Manufacture of the Product

The proposed method of manufacture is dry mixing and direct compression.
Validation has been performed on 3 industrial batches for each of the strengths. All the described parameters were consistent and within specifications. The process can then be considered as sufficiently validated.

- Product Specification

The product release and shelf-life specifications include tests for appearance (visual), identification (HPLC, UV, at release only), uniformity of dosage units (PhEur, at release only), average tablet weight (in-house, at release only), resistance to crushing (PhEur), friability (PhEur), disintegration (PhEur), dissolution (PhEur), assay (HPLC), related substances (HPLC), water content (Karl-Fischer) and microbiological quality (PhEur- Non-routine test).
Results from three industrial scale batches were provided for each strength. All presented batches comply with the proposed specification and demonstrate consistent manufacture.

- Adventitious Agents

None of the excipients are of human or animal origin.

- Stability of the Product

Three consecutive batches of each strength of Olanzapine Glenmark tablets have been stored under the following conditions and studied in stability studies: long-term (25°C ± 2°C, 60% RH ± 5% RH) for up to 18 months, accelerated (40°C ± 2°C, 75% RH ± 5% RH) for up to 6 months and intermediate Conditions (30°C ± 2°C, 65% RH ± 5% RH) up to 12 months. The stability studies are carried out in accordance with the current ICH/CPMP guidelines.
Except in accelerated conditions, where a significant increase of one identified impurity is observed with results out of specifications for the low strength, results in real time condition and intermediate conditions remain within specifications for all tested batches.
Photostability study according to the guideline was provided and from the results it can be concluded that the finished product is photostable when stored in the proposed packaging.

In conclusion the proposed shelf-life and storage conditions as stated in the SPC are accepted when the product stored in the proposed packaging.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-Clinical aspects

This application is made in accordance with Art 3(3) according to Regulation (EC) No 726/2004 "A generic medicinal product of a reference medicinal product authorised by the Community", Art 10 (1) "generic application" according to Directive 2001/83/EC, as amended by Directive 2004/27/EC.
No further non- clinical studies are required and the applicant justified why no such data was provided.

The pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well characterised.
The non-clinical overview, based on scientific literature on the pre-clinical pharmacology, pharmacokinetics and toxicology was considered adequate.

No environmental risk assessment is required as it is not anticipated that there will be additional use of products containing olanzapine as compared to current usage. Therefore it is considered that there is no additional risk to the environment from this medicinal product.

Discussion on Non-Clinical aspects

There are no non-clinical objections to approve Olanzapine Glenmark 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets.

2.4 Clinical Aspects

Introduction

This application concerns a generic medicinal product that contains six different strengths of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg olanzapine in tablets submitted by Glenmark Generics (Europe) Limited.

This application is made in accordance with Art 3(3) according to Regulation (EC) No 726/2004 "A generic medicinal product of a reference medicinal product authorised by the Community", Art 10 (1) "generic application" according to Directive 2001/83/EC, as amended by Directive 2004/27/EC. The reference medicinal product authorised for not less than 6/10 years in the EEA is Zyprexa 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg olanzapine in film-coated tablets from Eli Lilly Nederland BV (EU/1/96/022/002-019-023-029-004-020-024-030-011-006-025-031-008-009-010-026-032-012-021-027-033-014-022-028-034).

To support the application, the applicant has submitted one bioequivalence study (N^{o} 60679) with the intermediate strength of 10 mg and requested a biowaiver for other strengths.

Scientific advice was not sought for the development programme. For the clinical assessment the Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of relevance.

The SmPC is in line with that of the reference product Zyprexa.

GCP aspects

The bioequivalence study (BE) was conducted outside EU by a contract research organisation based in Canada. The study was compliant with GCP, as claimed by the applicant.

In accordance to Art 8(3)(ib) of the amended Directive, and Art 6.1 of the Regulation EC/726/2004, the applicant has provided a statement to the effect that clinical trials that were conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The French authorities (AFSSAPS) inspected the clinical and the analytical facilities in October 2002 with a positive outcome. Furthermore, those facilities were inspected by Portuguese authorities (INFARMED) and no major issues were raised.

Clinical studies

One bioequivalence study with olanzapine 10 mg tablets has been undertaken by the Sponsor Glenmark Pharmaceuticals Limited.

The bioequivalence study is the same for the concurrent application made for Olanzapine Glenmark Europe.

No specific clinical studies in patients were required in accordance with Article 10(1) of Directive 2001/83/EEC as amended. An appropriate literature review has been presented by the clinical expert supporting the use of olanzapine in the proposed indications, which are identical to those approved centrally for the reference product.

No safety clinical studies have been undertaken to support the application. The bioequivalence study provided some safety results that are discussed below.

Pharmacokinetics

- Methods

STUDY DESIGN

This was a single centre, open-label, single-dose, randomised, 3-way crossover bioequivalence study, performed under fasting conditions.

The objective of this study was to compare the rate and extent of absorption of olanzapine 10 mg tablets manufactured by Glenmark Generics Limited, India against Zyprexa 10 mg coated tablets (Eli Lilly, UK) and Zyprexa Velotab 10 mg orodispersible tablets (Eli Lilly, UK).

Subjects were confined to the clinical facility from at least 10 hours prior to drug administration, until after the 72-hour post-dose blood draw, in each period. The treatment phases were separated by washout periods of 21 days.

In each period, subjects received the test or one of the reference products (*Reference Product 1 – Zyprexa Velotab 10 mg orodispersible tablets; Reference Product 2 – Zyprexa 10 mg coated tablet*) as a single oral dose of one tablet containing 10 mg of olanzapine in the morning of Day 1. The bioequivalence study was performed under fasting conditions following a 10-hour overnight fast. Subjects were required to abstain from food or drink containing xanthine derivatives or xanthine-related compounds and energy drinks from 48 hours prior to drug administration and until the end of sample collection in each period (168-hour post-dose draw); alcohol-based products from 24 hours prior to drug administration and until the end of sample collection in each period, and food or beverages containing grapefruit or pomelo products, natural food supplements, and vitamins from 7 days prior to drug administration and until the end of sample collection in each period. Subjects were advised not to use soft or hard drugs or any tobacco products during the study. Vigorous physical activity was prohibited at all times during the confinements. Subjects were allowed to leave the clinical site after the 72-hour blood draw.

Zyprexa *(Reference Product 2)* was swallowed with a glass of water (240 ml).
The generic product (*Test product*) and Zyprexa Velotab (*Reference Product 1*) were administered by placing the tablet on the tongue for 2 minutes to allow disintegration and subsequently swallowed with 240 ml of water. Given that the modality of administration was different from the one described in the SmPC for tablets ("tablet should be swallowed with water") the CHMP expressed concern whether this modality of administration would impact the bioavailability of the generic product. In response the applicant stated that olanzapine was characterised by a slow absorption rate (t_{max} 4-8 hours), which indicated that the absorption rate was not determined by disintegration/dissolution of the tablets. It could be therefore assumed that water intake would have negligible influence on the pharmacokinetics of olanzapine from orodispersible tablets. The CHMP hence agreed that a BE study under such conditions would not be required as rapid disintegration of the tablets was shown.

Blood samples were collected prior to the study drug administration and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 120 and 168 hours post-dose. After centrifugation, the collected plasma aliquots were flash-frozen and stored at (-)80°C until analysis.

The protocol, the informed consent form and the amended informed consent form were approved by an independent ethics committee.

TEST AND REFERENCE PRODUCTS

Drug Code	Test	Reference 1	Reference 2
Formulation	Olanzapine 10 mg tablet	Zyprexa Velotab 10 mg (Olanzapine 10 mg orodispersible tablet)	Zyprexa 10 mg (Olanzapine 10 mg coated tablet)
Manufacturer	Glenmark Pharmaceuticals Ltd, India	Eli Lilly and Co, UK	Eli Lilly and Co, UK
Batch No.	Q13787002	A198432A	A310032
Manufacturing Date	09.2007	N/AV	N/AV
Expiry Date	08.2010 (proposed)	07.2009	08.2009

POPULATION STUDIED

Based on data from literature, the intra-subject coefficient of variation (CV) of olanzapine (by oral route) was expected to be approximately 8% and 15% for AUC and C_{max} respectively. Thus, assuming that the actual ratio of AUC and C_{max} is within 0.90 and 1.11, it was estimated that the minimum number of subjects to be included to meet the 80-125% confidence interval limits was about 26. Therefore, it was planned to include 30 subjects in order to allow for drop-outs.

A total of 30 subjects (11 females and 19 males) were included in the study. Subjects were healthy, adult non-smokers, aged $\geq$ 18 and $\leq$ 55 years with body mass indices $\geq$ 19.0 and $<$ 30.0 kg/m^2. Adequate inclusion/exclusion criteria were followed.

Twenty six patients finished the entire study and were included in the PK analysis. Two subjects withdrew for personal reasons and two other subjects were withdrawn due to adverse events. All withdrawals and drop-outs were adequately documented.

ANALYTICAL METHODS

A detailed and comprehensive description of the operative procedures is provided in the submitted documentation. A validation report is also provided.

PHARMACOKINETIC VARIABLES

For deriving pharmacokinetic parameters $AUC_{0\rightarrow t}$, AUC_{inf}, C_{max}, T_{max}, $T_{1/2}$, K_{el} a non-compartmental analysis was performed. AUC from the time of dosing to the last measurable concentration ($AUC_{0\rightarrow t}$) was calculated by mean of the linear trapezoidal rule. Extrapolation to infinity (AUC_{inf}) was calculated as a sum of $AUC_{0\rightarrow t}$ plus the ratio of the last measurable plasma concentration to the elimination rate constant.

STATISTICAL METHODS

The statistical part of the study was conducted using Win Nonlin software. Parametric ANOVAs on ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} was carried out. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect. A non parametric test (Friedman's Test) was carried out to compare T_{max}. Bioequivalence could be concluded if the 90 % CI of the ratio of the least square means of the test to reference products was within 80-125 % for AUC and C_{max}. No statement was made for T_{max}.

All these are conventional methods, and were therefore agreed by the CHMP.

- Results

The table below summarises the results on the pharmacokinetic parameters (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range) after a single 10 mg oral dose of olanzapine (n=26).

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test (S.D.)	493.3 (147.5)	523.7 (158.0)	11.4 (3.2)	4.5 (4.0)
Reference 1 (S.D.) **Zyprexa Velotab (**orodispersible tablet**)**	500.5 (142.3)	532.0 (153.6)	11.9 (3.0)	5.25 (2.5)
Reference 2 (S.D.) **Zyprexa (**coated tablet**)**	497.1 (139.7)	530.7 (149)	11.8 (3.0)	5 (2.39)
Test/Zyprexa Velotab ***Ratio (90% CI)** **Point estimate**	[95; 102]% 98%	[95; 101]% 98%	[91; 100]% 95%	ns
Test/Zyprexa ***Ratio (90% CI)** **Point estimate**	[95; 102]% 99%	[95; 102]% 98%	[92; 100]% 96 %	ns
Intra-subject CV (%)	7.6%	7.55%	9.7%	
Inter-subject CV (%)	31%	31.7%	24.3%	

$AUC_{0-\infty}$ 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 : median, min and max

**log-transformed values*

The mean K_{el} was 0.0174 $hours^{-1}$ for the test formulation, 0. 0169 $hours^{-1}$ for the reference product 1 (Zyprexa Velotab) and 0.0170 $hours^{-1}$ for the reference product 2 (Zyprexa). The mean $T_{1/2}$ value for the test and reference products were 40.6, 41.64 and 41.36 hours, respectively.

- Conclusions

The CIs of all PK parameters were within the acceptance range. Additionally the applicant provided satisfactory answers to the CHMP concerns on the modality of administration. Therefore, the bioequivalence of the generic product to the originator could be considered demonstrated for 10 mg tablets.

Protocol deviations (mainly blood sampling volume deviation and repeated blood pressure measurements) were judged to have no significant influence on bioequivalence assessment.

Transferability of study results to other strengths

The single bioequivalence study submitted by the applicant tested the 10 mg intermediate strength. Biowaiver was requested for the higher 20 and 15 mg as well the lower 7.5 mg, 5 mg and 2.5 mg strenghts in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), section 5.4. To grant a waiver the following criteria should be fulfilled:

1. The pharmaceutical products are manufactured by the same manufacturer and process;
2. The drug input has been shown to be linear over the therapeutic dose range;
3. The qualitative composition of the different strengths is the same;
4. The ratio between amounts of the active substance and excipients is the same;
5. The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

Not all these criteria were satisfied in the initial application. Hence, the CHMP requested further information. In particular:

20, 15, 7.5 and 5 mg Tablets:
For these strengths, the applicant was requested to demonstrate similarity of the *in vitro* dissolution at different pH values. The applicant provided all the requested dissolution profiles of all strengths in three media (pH 1.2, pH 4.5 and pH 6.8), showing that the formulation released 85% olanzapine within 15 minutes. The CHMP considered the answer satisfactory and concluded that these strengths can be considered bioequivalent to the originator.

2.5 mg tablets:
As the composition of 2.5 mg tablets was not quantitatively proportional to the tested 10 mg tablet and the amount of the active substance was not less than 5 % of the tablet core weight, a bioequivalence demonstration was requested for this strength. In response, the applicant provided dissolution profiles of 2.5 mg strength in three media (pH 1.2, pH 4.5 and pH 6.8), showing that the formulation released 85% olanzapine within 15 minutes. Therefore, given that the amount of active substance was only slightly above 5% (5.55%), the bio-waiver was accepted by the CHMP as all conditions to grant a biowaiver were considered to have been fulfilled.

Clinical Safety

A total of 139 post-dose adverse events were reported by 26 of the 30 subjects who received at least one dose of the study medication (safety population).

	Severity			Relation to the drug			
Treatment group	**Mild**	**Mod**	**Severe**	**Unrelated**	**Unlikely**	**Possible**	**Probable**
Test (A)	30	9	0	11	3	24	1
Zyprexa Velotab (B)	28	20	1	4	1	14	0
Zyprexa (C)	40	11	0	6	7	32	3
Total	98	40	1	21	11	70	4

According to the applicant, the adverse events reported in the three groups correspond to the ones listed within the SmPC for the reference product. These AEs are classified as very common (>1/10), common (1-10/100), or uncommon (1-10/1000) according to the MedDRA frequency.

Using the MedDRA classification as a base for comparison, the adverse events reported with test product are:
Very common – dizziness (5), headache (4), nausea (3), blood pressure decreased (4), heart rate decreased (3);
Common – diarrhoea (1), catheter related complication (1), catheter site erythema (1), catheter site pain (1), vessel puncture site haematoma (1), oral herpes (1), procedural dizziness (2), scratch (1), heart rate increased (1), back pain (1), somnolence (1), nasal congestion (2), pharangolaryngeal pain (2), rhinorrhea (1), erythema (1).

The adverse events reported with Zyprexa Velotab are:
Very common – dizziness (10), headache (10), blood pressure decreased (5), catheter site pain (3), somnolence (3);
Common – diarrhoea (1), lip dry (1), nausea (2), vomiting (1), energy increased (1), fatigue (1), vessel puncture site haematoma (2), oral herpes (1), alanine aminotransferase increased (1), heart rate decreased (1), insomnia (1), cough (1), dysphonia (1), nasal congestion (1), pharyngolaryngeal pain (2), rhinorrhea (2), erythema (1), hot flush (1).

The adverse events reported with Zyprexa Tablets are:
Very common – dizziness (4), headache (4), hot flush (3), back pain (3), blood pressure decreased (4);
Common – ocular hyperaemina (1), abdominal distension (1), diarrhoea (1), dry mouth (1), flatulence (1), hypoaesthesia (1), nausea (2), asthenia (2), catheter site erythema (1), vessel puncture site haematoma (1), vessel puncture site reaction (1), thirst (1), foot fracture (1), heart rate decreased (1),

heart rate increased (1), decreased appetite(1), musculoskeletal stiffness (1), myalgia (1), dysarthria (1), hypoaesthesia (1), syncope (1), tremor (1), cough (2), pharangolaryngeal pain (2), rhinorrhea (1), throat irritation (1)

There were no deaths or serious adverse events reported. Two subjects were withdrawn from the study due to adverse events, i.e. one subject due to syncope and decreased blood pressure, the other one due to vomiting.

The safety data collected from the bioequivalence study do not reveal any clinically significant safety issues with this generic product.

Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for all strengths should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

The company should ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product. Therefore, the MAH should commit to the subsequent follow-up or other measures:

1. The MAH should further continue to monitor and review in the PSURs:

- reports of patients younger that 18 years old;

- reports of patients receiving long-term (>1 year) treatment with olanzapine should be continued;

- reports on myocarditis, cardiomyopathy and myocardial damage in association with olanzapine treatment.

2. The MAH should continue to monitor following reports as a part of routine pharmacovigilance activities:

- serious haematological reactions in association with olanzapine treatment;

- venous thromboembolism in association with olanzapine treatment;

- rhabdomyolysis in association with olanzapine treatment;

- pregnancy and lactation in patients exposed to olanzapine;

- hypothyroidism and hyponatraemia/SIADH/Diabetes insipidus;

- serotonin syndrome;

- drug interaction;

- glucose dysregulation in patients < 18 years of age.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

Discussion on Clinical aspects

To support the application, 1 bioequivalence study with 10 mg of olanzapine was submitted (N° 60679). The study was designed according to a randomised, open-label, single-dose, three-way, two-period, two-sequence crossover scheme.

Of the 30 subjects enrolled 26 received the two treatments and were included in the statistical analysis. Four subjects were withdrawn from the study either for personal reasons or due to adverse events (please see below). The number of subjects included in the study was sufficient.

The bioequivalence study was performed under appropriate conditions and in line with applicable guidelines.

The results of the bioequivalence study showed that the conventional confidence intervals for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for olanzapine were within the acceptance range of 80-125%. No significant difference in T_{max} was evidenced by the non-parametric test. Therefore, based on the available data it was concluded that bioequivalence of the two products had been demonstrated.

The extrapolation of the bioequivalence study results obtained for the 10 mg olanzapine tablets to the 2.5 mg, 5 mg, 7.5 mg, 15 mg and 20 mg tablets was deemed acceptable following the results of additional dissolution studies demonstrating similar dissolution profiles of all tested strengths (please see above). Consequently, all criteria for a biowaiver listed in the applicable guidance were considered fulfilled.

A number of post-dose adverse events were reported in the safety population. Two subjects were withdrawn from the study due to adverse events, i.e. one subject due to syncope and decreased blood pressure, the other one due to vomiting. These adverse events were judged to be possibly related to study medication and resolved spontaneously. The safety concerns with the use of olanzapine have been addressed in the SmPC with the inclusion of appropriate warnings, precautions, and contraindications, and are in line with the reference product. Moreover, the applicant has committed to monitoring and reviewing in the PSURs the safety concerns observed also for the reference product.

- **User consultation**

The results of user consultation provided indicates that the Package leaflet is well structured and organized, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable in patients /users are able to act upon the information that it contains.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

This application was made in accordance with Art 3(3) of Regulation (EC) No 726/2004 "A generic medicinal product of a reference medicinal product authorised by the Community" and Art 10(1) "generic application" of Directive 2001/83/EC. The reference medicinal product is Zyprexa. According to the legal basis, no non-clinical studies were required. The applicant provided an appropriate non-clinical overview of olanzapine based on scientific literature. No additional clinical trials were required except for bioequivalence studies. The clinical overview provided an adequate summary of clinical data for olanzapine. The results of the bioequivalence study demonstrated the bioequivalence of Olanzapine Glenmark 10 mg tablets and the reference products (Zyprexa 10 mg film-coated tablet and Zyprexa Velotab 10 mg orodispersible tablet). The extrapolation of the study results to lower strengths of olanzapine, i.e. 2.5 mg, 5 mg, 7.5 mg as well as higher strengths of 15 mg and 20 mg was considered acceptable. The adverse events in the bioequivalence study were comparable to the reference product and no serious adverse events were observed.

The application contained adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the originator was therefore concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Olanzapine Glenmark 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets in the following indications in adults:
- treatment of schizophrenia; olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response;
- 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;
was favourable and therefore recommended the granting of the marketing authorisation.