EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc. Ref.: EMA/186276/2010
Evaluation of Medicines for Human Use

Assessment Report

Olanzapine Apotex

International Non-proprietary Name: olanzapine

Procedure No. EMEA/H/C/001178

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Apotex submitted on 06 May 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Olanzapine Apotex, 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'.

At the time of submission, the applicant applied for 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg film coated tablets and 5, 10, 15 and 20 mg orodispersible tablets under Article 10 (1) (Generic medicinal product) of Directive 2001/83/EC . The 15 mg and 20 mg film-coated tablets presentations were withdrawn during evaluation by the applicant.

The application legal basis 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 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg coated tablets
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 27 September 1996
- Marketing authorisation granted by: Community
    - Marketing authorisation number: EU/1/96/022, all numbers to be included.

■ 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:

Film-coated tablets:

- Product name, strength, pharmaceutical form: Zyprexa 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg coated tablets
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 27/09/1996
- Marketing authorisation granted by: Community
    - Marketing authorisation number(s): EU/1/96/022, all numbers to be included.
- Bioavailability study number(s): OLAN-IMTB-05SB02-2FA-(1)

Orodispersible tablets:

- Product name, strength, pharmaceutical form: Zyprexa Velotab 5, 10, 15 and 20 mg orodispersible tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 03/02/2000
- Marketing authorisation granted by: Community
    - Marketing authorisation number(s): EU/1/99/125
- Bioavailability study number(s): OAN-P8-571

■ Medicinal Product used for bioequivalence study:

- Product name, strength, pharmaceutical form: Zyprexa 10 mg coated tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Member State of source: United Kingdom
- Product name, strength, pharmaceutical form: Zyprexa Velotab 10 mg orodispersible tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Member State of source: United Kingdom

The Rapporteur appointed by the CHMP and the evaluation team was:

Rapporteur **Dr John J Borg**

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 EMA on 06 May 2009.
- The procedure started on 27 May 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2009.
- During the meeting on 21 – 24 September 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 24 September 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2009.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 February 2010.
- During the CHMP meeting on 15 – 18 February 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During the meeting on 15 – 18 March 2010, 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 Apotex on 18 March 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 March 2010.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Olanzapine Apotex 2.5 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets and 5, 10, 15 and 20 mg orodispersible tablets are a generic medicinal product containing olanzapine as the active substance.

At the time of submission, the applicant also proposed additional strengths of 15 mg and 20 mg film-coated tablets but these were subsequently withdrawn by the applicant during the evaluation procedure.

The reference products are Zyprexa and Zyprexa Velotab which have been centrally authorised on 27 September 1996 and 3 February 2000, respectively.

Olanzapine, a thienobenzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. Atypical antipsychotics have greater affinity for serotonin 5-HT_{2A} receptors than for dopamine D_2 receptors and cause fewer extrapyramidal symptoms (EPS) and improve negative symptoms in contrast to classical antipsychotics such as haloperidol.

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 Apotex is the same as for the authorised Reference medicinal product Zyprexa.

Olanzapine is indicated for the treatment of schizophrenia. Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Olanzapine is indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, it is indicated for the prevention of recurrence in patients with bipolar disorder.

2.2 Quality aspects

Introduction

Olanzapine Apotex is presented as film-coated tablets and orodispersible tablets.

The film coated tablets contain 2.5 mg, 5 mg, 7.5 mg and 10 mg of olanzapine as active substance. The other ingredients are lactose monohydrate, microcrystalline cellulose, maize starch and magnesium stearate. The film coating consists of hypromellose, hydroxypropylcellulose, macrogol 8000 and titanium dioxide.

The orodispersible tablets contain 5 mg, 10 mg, 15 mg, and 20 mg of olanzapine as active substance. Other ingredients are mannitol, microcrystalline cellulose, carmellose calcium, sucralose, magnesium stearate and silica colloidal anhydrous.

The film-coated tablets and orodispersible tablets are marketed in aluminium/aluminium blisters packed in cartons.

Active substance

The active substance is olanzapine and its chemical name is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5] benzodiazepine according to the IUPAC nomenclature.

The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44 g/mol.

Olanzapine structural formula is as follows:

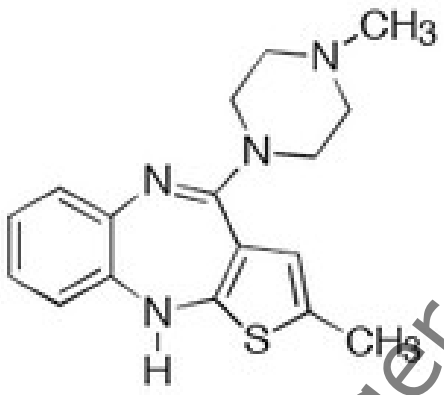

Figure 1: Chemical structure of Olanzapine

Olanzapine is not yet described in the Ph.Eur, and it is routinely controlled by in-house monograph. It was noticed that all the relevant information for this active substance has been provided.
Olanzapine is pale yellow to yellow crystalline powder. Olanzapine is insoluble in water, freely soluble in dichloromethane, soluble in acetone, soluble *n*-propanol and sparingly soluble in 2-butanol and in acetonitrile. Slightly soluble in methanol and in dehydrated alcohol. It shows polymorphism. However, only one form will be used in the manufacturing of this medicinal product.
Olanzapine is sensitive to acid and basic hydrolysis, oxidation and humidity. This active substance does not contain chiral centres. Therefore, does not exhibit stereoisomerism.

- **Manufacture**

Olanzapine is synthesised in two reactions steps. The manufacturing process has been adequately described in the Active Substance Master File. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. Potential impurities have been well discussed in relation to their origin and potential carry-over into the final active substance.
Structure elucidation has been performed by infrared absorption spectroscopy, ultraviolet spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, and mass spectroscopy. The molecular weight was determined by elemental analysis.

- **Specification**

The active substance specifications include tests for appearance (light yellow powder), identification (PXRD/IR/UV), loss on drying, Related Compounds (HPLC and GC), residual solvents (GC), assay (titration), and residue on ignition, heavy metals, and particle size (laser diffraction).
It was verified that all specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.

Impurities were described, classified as process related impurities and possible degradation products, and specified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term (25°C/60%RH) and accelerated studies (40°C/75%RH) were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: appearance, identification (IR), assay (titration), related compounds (HPLC and GC) and loss on drying. It was noticed that the test methods applied are those used for release of the active substance.
It can be concluded that the proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material protected from exposure to moisture, air and light.

Medicinal product

Film coated Tablets

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the applicant was to develop a medicinal product bioequivalent to the reference product (Zyprexa). Taking into account the rapid dissolution characteristics exhibited by the originator Zyprexa tablets; the objective was also to develop generic film coated tablets that had immediate release properties.
These objectives were achieving by combining the active substance with some excipients that have been selected. In order to optimise the physico-chemical properties of these tablets a series of experimental studies were conducted varying excipients. All modifications in the formulation were done until a satisfactory formulation was found. All the excipients used are well known and commonly used in the pharmaceutical industry. The proposed formulation is proportional among the 2.5 mg, 5 mg, 7.5 mg and 10 mg strengths, so a single blend was manufactured and divided amongst the lowest (2.5 mg) and highest (10 mg) strengths to evaluate the manufacturing process.
Comparative dissolution profiles at three different media were provided. The results demonstrated that the generic batches used for the bioequivalence studies, generic stability batches and the EU brand leader batches are similar with respect to dissolution rate.

- **Adventitious Agents**

Among excipients used in the finished product only lactose monohydrate present is of animal origin. Declarations from lactose suppliers were provided stating that milk used for production of lactose is sourced from healthy animals under the same conditions as milk collected for human consumption. Magnesium stearate used in this formulation is of vegetable origin.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as blending, direct compressing and coating.

Furthermore, the equipment used is commonly available in the pharmaceutical industry. The critical steps in the manufacturing process have been identified and controlled.

It was noticed that the manufacturing process has been adequately validated for three pilot scale batch of each strength and the results of the manufacturing validation reports were considered satisfactory.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance (visual), identification (HPLC and UV), titanium dioxide identification, average weight, dissolution (HPLC), assay (HPLC), uniformity of dosage unit, degradation products (HPLC), water content and microbial limits.

Degradation products were identified and controlled.

All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.

The batch analysis data for three pilot scale batches of each strength confirm that the tablets can be manufactured reproducibly according to the agreed finished product specifications.

- **Stability of the Product**

Three batches of each strength (2.5mg, 5mg, 7.5mg and 10mg) of the film-coated tablets packed in intended market containers were placed on stability under ICH conditions 25º C/60% RH for 36 months, 30º C/65% RH for 12 months and 40º C/75% RH for 6 months. It was verified that the following parameters were controlled: assay, degradation products, dissolution, appearance and identification.

Photostability study was performed on one batch of all strengths of film-coated tablets stored according to Note of Guidance on photostability test. No significant change was observed in the finished product as result of direct exposure to light. It was noticed that one batch of 2.5 mg, and 10 mg was stored under stress conditions (thermal; acidic conditions, basic conditions, oxidative conditions and light)
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Orodispersible tablets

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to develop a medicinal product bioequivalent to the reference product (Zyprexa Velotab). In this context, several studies were conducted in order to find orodispersible tablets formulation with rapid dissolving properties across physiological pH range, disintegration in water in less than 60 seconds, meeting the general physical and chemical specifications for orodispersible tablets and meeting the general requirements of the relevant guidelines. These objectives were achieved by combining the active substance with some excipients that have been selected. In order to optimise the physico-chemical properties of these orodispersible tablets a series of experimental studies were conducted varying excipients. All modifications in the formulation were done until a satisfactory formulation was found. All the excipients used are well known and commonly used in the pharmaceutical industry.
The proposed formulation is proportional among the 5 mg and 10 mg, 15 mg, 20 mg strengths.
Comparative dissolution profiles at three different media were provided. The results demonstrated that the generic batches used for the bioequivalence studies, generic stability batches and the EU brand leader batches are similar with respect to dissolution rate.

- **Adventitious Agents**

None of the excipients used in the manufacturing of Olanzapine orodispersible tablets are of human or animal origin. Magnesium stearate used in this formulation is of vegetable origin.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, dry granulation and compressing.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. The critical steps in the manufacturing process have been identified and controlled. It was noticed that the manufacturing process has been adequately validated for three pilot scale batch of each strength and the results of the manufacturing validation reports were considered satisfactory.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance (visual), identification (HPLC and UV), average weight, dissolution, disintegration, assay (HPLC), uniformity of dosage unit, degradation products (HPLC), water content and microbial limits.
All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
Batch analysis data was provided on three pilot scale batches for each strength of the finished product. Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. It has been shown that orodispersible tablets can be manufactured reproducibly according to the finished product specifications.

- **Stability of the Product**

Three batches of 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets packed in intended market containers were placed on long term, intermediate and accelerated stability under ICH conditions 25º C/60% RH for 36 months, 30º C/65% RH for 12 months and 40º C/75% RH for 6 months. It was verified that the following parameters were controlled: appearance, identification (IR), assay, degradation products (HPLC/GC), dissolution and microbial limits.
Photostability study was performed on one batch of 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets stored according to Note of Guidance on photostability test. No significant change was observed in the finished product as result of direct exposure to light. It was noticed that one batch of 5 mg and 20 mg was stored under stress conditions (thermal; heat/humidity and light).
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic. Dissolution results indicate comparability with the reference product (Zyprexa & Zyprexa Velotab) and this is confirmed by in-vivo bioequivalence results (see the clinical part of the report). At the time of the CHMP opinion, there is a minor unresolved quality issue, which does not have any impact on the benefit/risk ratio of the medicinal product. This will be addressed as part of the follow-up measures to be addressed post-authorisation. In this context, it can be concluded that the quality characteristics of the finished product are adequate and 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.

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 were no non-clinical major objections to approve Olanzapine Apotex film-coated tablets and orodispersible tablets.

2.4 Clinical Aspects

Introduction

This application initially concerned a generic medicinal product that contains the following strengths and pharmaceutical forms: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg as film-coated tablets and 5 mg, 10 mg, 15 mg and 20 mg as orodispersible tablets.

To support this application, the applicant has submitted two bioequivalence studies conducted with the intermediate strength of 10 mg and using the two different proposed pharmaceutical forms : study 1 (OL 5063) for the film coated tablets and study 2 (OAN-P8-571) for the orodispersible tablets.

Exemption

In accordance with the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the applicant considered that the criteria for a biowaiver are met for the following strengths and pharmaceutical forms: 2.5 mg, 5 mg, 7.5 mg, 15 mg and 20 mg as film-coated tablets and 5 mg, 15 mg and 20 mg as orodispersible tablets.

The results of the study 2 (OAN-P8-571) could be extrapolated to the other strengths 5 mg, 15 mg and 20 mg orodispersible tablet strengths, according to the conditions listed in the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). The dissolution data presented by the applicant with respect to the orodispersible tablet strength series being applied for fully supported the biowaiver for these additional strengths.

However the results of the study 1 (OL5063) could not be extrapolated to Olanzapine Apotex 15 mg and 20 mg film-coated tablet strengths, as the composition of Olanzapine Apotex 15mg and 20 mg film-coated tablets was not quantitatively proportional to the tested Olanzapine Apotex 10 mg film coated tablet strength and as the amount of active substance in these tablets was not less than 5 % of the tablet core weight. Therefore bioequivalence at these strengths could not be waived as one of the condition listed in the NfG on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, was not met, namely, the ratio between amounts of active and excipients is the same. Following a Major Objection raised by the CHMP in this regards, the applicant withdrew its application for 15 mg and 20 mg film coated tablet strengths.

The applicant has concluded similarity for the dissolution profiles of the remaining strengths of test and reference products in pH 4.5 and 6.8 phosphate buffer and for the dissolution profiles of the test bioequivalence batch of Olanzapine Apotex 10 mg versus the additional strengths of the test product in pH 4.5 and 6.8 phosphate buffer. In the CHMP's view, the results of study 1 (OL5063) could be extrapolated to the 2.5 mg, 5 mg, and 7.5 mg film coated tablet strengths.

Clinical studies

Two bioequivalence studies were conducted: study 1 (OL 5063) for the film coated tablets and study 2(OAN-P8-571) for the orodispersible tablets.

Pharmacokinetics (PK)

Film-coated tablets study 1 (OL 5063)

- **Methods**

STUDY DESIGN

The study [protocol number: OLAN-IMTB-05SB02-2FA-(1)] was an open-label, single-dose, comparative, randomized, 2-way crossover bioavailability study of Olanzapine tablets, 10mg (Apotex Inc.) and Zyprexa tablets, 10mg (Eli Lilly and Company Limited). The study was conducted in Canada in 23 healthy male and female volunteers, under fasting conditions, with a wash-out period of 3 weeks. The bioanalytical, pharmacokinetics and statistical analyses were performed in India.

The study was performed from 26 July 2008 to 21 August 2008. Subjects were randomly assigned to a treatment according to the computer generated randomization scheme.

A total of 21 blood samples were taken from each subject during each treatment period at the following pre-defined time-points: 2 samples taken 5 to 45 minutes prior to dosing (0) and 1 sample each at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours after dosing. Olanzapine was the analysed compound.

Plasma Samples were analysed between the 1 and 8 September 2008. Laboratory analysts were blinded to the samples as these were identified only by subject identification number, period number and sampling time, and were not allowed access to the randomization scheme.

The study report, dated 3 November 2008 has a statement indicating that this study, including the archiving of essential documents, was carried out in compliance with the ICH-GCP. In Module 1.9 the applicant also stated that this study was conducted in accordance with ICH GCP. The protocol was approved by an institutional review board called Research Ethic Board (REB) on 29 May 2008 and further revision was approved on 7 July 2008.

TEST AND REFERENCE PRODUCTS

Olanzapine Apotex 10mg film-coated tablets by Apotex Inc, Canada (batch No. FD096-74, manufacturing date February 2008, expiry date: February 2010) has been compared to Zyprexa 10mg coated tablets (Eli Lilly and Company Limited, batch No: A424227, sourced from the UK market, expiry date: July 2010).

Relevant data of the test and reference product is summarised in the following table:

	TEST PRODUCT	REFERENCE PRODUCT
Name, strength & pharmaceutical form	Olanzapine Apotex, 10mg Film-coated tablets	Zyprexa, 10mg Coated tablets
Applicant or MAH	Apotex Inc, Canada	Eli Lilly and Company Limited, United Kingdom
Date of authorisation in the EU	Not applicable	27 September 1996
Batch number	FD096-74	A424227
Country of origin	Canada	United Kingdom
Date of manufacture	17 February 2008	Not available
Expiry date	February 2010	July 2010
Assayed content	99.7%	99.3%

POPULATION STUDIED

Twenty three healthy subjects (10 males and 13 females), of multiple ethnic origins (4 black, 7 asian, 6 caucasians, 4 hispanic/latino and 2 multiracial), non-smokers, aged between 23 and 49 years, with an average BMI of 24.4 kg/m^2 (range 19.0 – 29.1), were dosed in the study. Of these, 17 subjects (7 males and 10 females) completed the studyReasons for withdrawal of the 6 subjects was given as follows:

- One subject was withdrawn by the clinician during period 1 due to an adverse event (ECG changes - accelerated junctional rhythm and ectopic atrial beats) sustained 2 to 4 hours post-dosing with reference drug and considered as unlikely related to the reference drug which had been administered.
- One subject who had been administered the test drug in period 1, was withdrawn in between periods due to missed period 1, 96 and 120 hour ambulatory visits, since it was decided that the absence of these missed samples could result in a loss of AUC of approximately 20% and hence could significantly impact the assessment of AUCt.
- One subject who had been administered the test drug in period 1, voluntarily withdrew in the inter-period.
- One subject was withdrawn at period 2 check-in prior to dosing, on discovery of a pre-dose presyncopal event with ECG sinus bradycardia and first degree AV block experienced prior to dosing with test drug in period 1. On retrospect, inclusion of this patient was considered as a protocol violation.
- One subject voluntarily withdrew after the 8 hour blood draw of period 2 in which he had been administered the test drug.
- One subject was withdrawn prior to period 2 dosing due to the discovery of an adverse event (elevated Creatinine Kinase) experienced 72 hours after dosing with reference product in period 1. Retrospectively this adverse event was considered possibly related to the reference drug.

Of the 17 subjects who completed the study, one subject was found to have significant pre-dose concentrations of olanzapine in Period 1 and was excluded from the PK and statistical analysis in accordance with the protocol. Primary PK and statistical analysis were therefore carried out on the remaining 16 subjects who completed the study.

ANALYTICAL METHODS

Olanzapine concentrations were measured by a solid phase extraction method with LC-MS/MS technique. Results of pre-study and within study have sufficiently been provided for specificity, accuracy, precision, limit of quantification, response function, and stability of the stock solution and analyte in human plasma under processing conditions to consider the method validated.

PHARMACOKINETIC VARIABLES

The following PK variables were calculated: AUCt (area under the plasma concentration-time curve from time zero to t hours) calculated by the linear trapezoidal rule, AUCinf (area under the plasma concentration-time curve from time zero to infinity), Cmax (maximum plasma concentration), Tmax (time for maximum concentration), Kel (elimination rate constant), and Thalf (half-life).

STATISTICAL METHODS

Analysis of variance (ANOVA) was performed on the log-transformed AUCt, AUCinf and Cmax parameters and on the untransformed Tmax, Kel and Thalf parameters (Proc GLM of SAS). The ANOVA included sequence, subjects nested within sequence, period and treatment as factors. Tmax data was also analyzed by a non-parametric method (Wilcoxon Rank Sum Test).

The least-squares means for the treatments and the adjusted differences between the treatment means were estimated. The 90% confidence interval for the ratio between the test and reference means was constructed.

Criteria for bioequivalence were set such that the 90% confidence interval (90% CI) of the relative mean AUCt and AUCinf of the test to reference formulation should be within 0.80 -1.25. A wider 90% confidence interval for Cmax was set and justified a priori in the protocol. Thus Bioequivalence for Cmax was to be declared if the 90% confidence interval of the relative mean Cmax of the test to reference formulation should fall within 0.75 -1.33.

- **Results**

The pharmacokinetic results are shown in Table 1.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	539.46 (117.18)	609.29 (145.66)	14.93 (3.53)	5.02 (1.50 – 10.04)	39.44 (7.62)
Reference	530.91 (114.51)	599.15 (141.47)	15.76 (4.54)	5.00 (2.00 – 10.07)	39.67 (8.41)
***Ratio (90% CI)**	1.02 (0.98 – 1.05)	1.02 (0.98 – 1.05)	0.96 (0.91 – 1.02)		
CV (%)	5.3	5.9	8.9	32.8	8.5

$AUC_{0-\infty}$ 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*

A total of seventy-nine (79) mild adverse events occurred in nineteen (19) subjects after they received the test preparation. A total of eighty-two (82) mild adverse events occurred in nineteen (19) subjects after they received the reference preparation. These events were judged by the clinician as to their severity, causality and relationship to the administered drug.

No deaths or serious adverse events were reported in this study.

- **Conclusions**

Based on the presented bioequivalence study 1 (OL5063), Olanzapine Apotex, 10mg film-coated tablets is considered bioequivalent with Zyprexa 10 mg coated tablets. On the basis of the data provided by the applicant on dissolution profile and considering the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results of study 1 (OL5063) could be extrapolated to the 2.5 mg, 5 mg, and 7.5 mg film coated tablet strengths.

Orodispersible tablets study 2 (OAN-P8-571)

- **Methods**

STUDY DESIGN

The study [protocol number: OAN-P8-571] was a single-dose, comparative, randomized, 2-way cross over bioavailability study of Olanzapine Orally Disintegrating Tablets 10 mg (Apotex Inc) and Zyprexa Velotab 10 mg, Orodispersible Tablets (Eli Lilly Netherlands) in 22 healthy male and female volunteers, under fasting conditions, with a wash-out period of 21 days. The bioanalytical, pharmacokinetics and statistical analyses were performed in Canada.

The study was conducted from 19 August 2008 to 2 October 2008. Subjects were randomly assigned to a treatment according to the computer generated randomization scheme.

A total of 20 blood samples were taken from each subject during each treatment period, at the following pre-defined time-points: prior to dosing (0) and 1 sample each at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours after dosing. Olanzapine was the analysed compound.

Plasma samples were analysed between the 23 September and 6 October 2008. Laboratory analysts were blinded to the samples.

The study report, dated 26 November 2008 has a statement stating that this study, including the archiving of essential documents, was carried out in compliance with Good Clinical Practice (GCP). In Module 1.9 the applicant also stated that this study was conducted in accordance with ICH GCP. The protocol was approved by an institutional review board (ETHIPRO) on 13 August 2008 and further revision on the informed consent form was approved on 18 August 2008.

TEST AND REFERENCE PRODUCTS

Olanzapine Apotex, 10mg orally disintegrating tablets by Apotex Inc, Canada (batch No. FD061-59, manufacturing April 2008, expiry date: April 2010) has been compared to ZYPREXA Velotab 10mg orodispersible tablets (Eli Lilly Netherlands, The Netherlands), batch No:753380D, sourced from the UK market, exp. date October 2010).

Relevant data of the test and reference product is summarised in the following table:

	TEST PRODUCT	REFERENCE PRODUCT
Name, strength & pharmaceutical form	Olanzapine Apotex, 10mg orally disintegrating tablet	Zyprexa Velotab, 10mg orodispersible tablet
Manufacturer	Apotex Inc, Canada	Eli Lilly Netherlands, The Netherlands
Date of authorisation in the EU	Not applicable	3rd February 2000
Batch number	FD061-59	753380D
Country of origin	Canada	United Kingdom
Date of manufacture	April 2008	Not available
Expiry date	April 2010	October 2010
Measured content	99.4 % of label claim	99.6 % of label claim

POPULATION STUDIED

Twenty-two healthy subjects (17 males and 5 females), mainly white (3 black), non- or ex- smokers, aged between 22 and 45 years, with an average BMI of 26.4 kg/m^2 (range 24.3 to 29 kg/m^2), were dosed in the study. Of these, 20 subjects (17 males and 3 females) completed the study. All withdrawn samples from all patients were assayed but statistical analysis was performed only on the 20 subjects who completed the study.

Reasons for withdrawal of the 2 subjects were given as follows:

- One subject was withdrawn after dosing with test product in period 2 due to vomiting 2 hours post-dose since this could have interfered with the PK profile characterization
- One subject was withdrawn prior to dosing with the test product in period 2 due to a decrease in systolic blood pressure (safety reason)

ANALYTICAL METHODS

Olanzapine concentrations were measured by a solid phase extraction HPLC method with MS/MS detection. Results of pre-study and within study have sufficiently been provided for specificity, accuracy, precision, limit of quantification, response function, and stability of the stock solution and analyte in human plasma under processing conditions to consider the method validated.

PHARMACOKINETIC VARIABLES

The following PK variables were calculated: AUCt calculated by the trapezoidal rule, AUCinf, Cmax, Tmax, Kel, and Thalf.

STATISTICAL METHODS

Pharmacokinetic and statistical analyses were generated using Kinetic, version 8.00, and SAS version 9.1 of the pharmacokinetic facility.

Analysis of variance (ANOVA) was performed on the log-transformed AUCt, AUCinf and Cmax parameters and on the untransformed Tmax, Kel and Thalf parameters (Proc GLM of SAS). The ANOVA included sequence, subjects nested within sequence, period and treatment as factors.

Criteria for bioequivalence were set such that the 90% confidence interval of the relative mean AUCt and AUCinf of the test to reference formulation should be within 80 to 125%. A wider 90% confidence interval for Cmax was set and justified a priori in the protocol. Thus bioequivalence for Cmax was to be declared if the 90% confidence interval of the relative mean Cmax of the test to reference formulation should fall within 75 to 133%.

- **Results**

The pharmacokinetic results are shown in Table 2.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	526.37 (138.56)	587.28 (164.48)	13.60 (3.06)	5.50 (2.00 – 7.00)	34.85 (7.05)
Reference	526.50 (136.80)	594.65 (179.78)	13.72 (3.84)	6.00 (1.50 – 8.00)	37.81 (7.88)
***Ratio (90% CI)**	100.15 (96.14 – 104.33)	99.63 (95.52 – 103.92)	99.75 (95.67 – 104.00)		
CV (%)	7.4	7.7	7.6		

$AUC_{0-\infty}$ 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*

All twenty-two (22) subjects experienced a total of ninety-one (91) adverse events during the study. All except one event were considered as at least possibly drug related. Of these, forty-two (42) adverse events (13 different types) were reported after the single dose administration of the Test product and fifty (50) adverse events (13 different types) were reported after the single dose administration of the Reference product. Two (2) adverse events associated with post-study laboratory test results (neutrophil count decreased (2 episodes)) were imputed to both formulations. These events were classified as 32 mild, 55 moderate, and 4 severe. However none of these events were considered to be unexpected or required the use of concomitant medication.

No deaths or serious adverse events were reported in this study.

- **Conclusions**

Based on the presented bioequivalence study 2 (OAN-P8-571), Olanzapine Apotex, 10mg orally disintegrating tablets is considered bioequivalent with Zyprexa Velotab 10 mg orodispersible tablets. On the basis of the data provided by the applicant on dissolution profile and considering the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) , the results of study 2 (OAN-P8-571), could be extrapolated to the 5 mg, 15 mg and 20 mg as orodispersible tablets.

Pharmacodynamics

No new data has been provided, which was considered acceptable by the CHMP since bioequivalence has been shown by pharmacokinetic studies in order to substantiate therapeutic equivalence.

Additional data

The applicant has presented comparative dissolution profiles for the biobatches (i.e. 10mg film coated tablet and 10 mg orodispersible tablet strengths respectively) and the additional strengths (i.e. 2.5 mg, 5 mg, 7.5 mg, 15 mg, 20 mg film coated tablet strengths and 5 mg, 15 mg and 20 mg orodispersible tablet strengths respectively) at 3 different pHs. Data showed that dissolution profiles are similar for all strengths in 0.1N HCl, 0.05M phosphate buffer pH 4.5 and pH 6.8.

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 Olanzapine Apotex film-coated tablets and orodispersible tablets should follow PSURs submission schedule for the reference medicinal product.

The next PSUR submission of the reference medicinal product is due by 31 May 2010.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described in version 5.0 by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before and whilst the product is on the market.

- **Risk Management Plan**

A Risk Management Plan was not submitted. Since the application concerns a generic of reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified, a Risk Management Plan was not required.

- **User consultation**

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

Discussion on Clinical aspects

Bioequivalence has been adequately demonstrated in studies 1 (OL 5063) and 2 (OAN-P8-571) for both film coated and orodispersible 10 mg formulations of Olanzapine Apotex. In these two studies, the studied population, pharmacokinetic variables and statistical methods were considered acceptable by the CHMP.

On the basis of the data provided by the applicant on dissolution profile and considering the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results of both studies 1(OL 5063) and 2 (OAN-P8-571), could be extrapolated to the 2.5 mg, 5 mg, and 7.5 mg film coated tablet strengths and the 5 mg, 15 mg and 20 mg as orodispersible tablets, respectively.

In study 1 (OL 5063), a rather high withdrawal rate (26%) was experienced. However the number for all withdrawals and the remaining number of subjects on whom the PK and statistical analysis was conducted is greater than the minimum recommended by the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Two subjects were withdrawn from the study due to protocol deviations.

The 90% confidence intervals of the test/reference (T/R) ratio lie well within the 80 – 125% BE acceptance limits for AUCt, AUC_{∞} and Cmax. Mean extrapolation of AUC was 11% for both test and reference products. The extrapolated AUC was only marginally greater than 20% (20.83%) in only one subject for the reference product, which was acceptable by the CHMP.

No pre-dose levels of olanzapine were detected in any of the samples included in the PK analysis. Tmax was not observed in any of the first sample times. All Cmax values were greater than 37 times

the Lower Limit of Quantification (LLOQ) and fell within the validated range. Therefore Cmax has been well characterised.

One subject was excluded from the primary PK and statistical analysis because an unexplained significant pre-dose concentration of olanzapine was detected in Period 1. This amounted to approximately 11% of Cmax experienced by the same subject in the same period. However, the point estimates and 90% confidence intervals of the test/reference (T/R) ratios with the inclusion of this subject were largely unchanged. Values were 1.01 (0.98 – 1.04) for AUCt, 1.01 (0.97 – 1.05) for AUC_{∞}, and 0.96 (0.91 – 1.01) for Cmax.

A high number of cardiac related events were reported including sinus bradycardia events in subjects following both test and reference products. A few of the cases of sinus bradycardia occurred in the first 4 hours following dosing, but most occurred around 24 hours after dosing. These were all considered as unlikely related to administered drug by the applicant. Such events are already reflected in the Product Information of the reference medicinal product.

In study 2 (OAN-P8-571), the 90% confidence intervals of the test/reference (T/R) ratio lie well within the 80 – 125% BE acceptance limits for AUCt, AUC_{∞} and Cmax. Mean extrapolation of AUC was <11% for both test and reference products. The extrapolated AUC was only marginally greater than 20% (20.18%) in only one subject for the test product which was considered acceptable by the CHMP.

No pre-dose levels of olanzapine equal to or greater than the LLOQ were detected in any of the samples included in the PK analysis. Tmax was not observed in any of the first sample times. All Cmax values were greater than 86 times the LLOQ. One Cmax value was higher than the Upper Limit of Quantification (ULQ) but this is covered by the dilution integrity validation. In conclusion, Cmax has been well characterised.

There were no identifiable safety concerns for the test product and the results indicated that there were no quantifiable differences between the AE profile of test and reference product.

Overall, the safety of olanzapine is well documented and both test and reference products have a comparable adverse event profile.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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

Recommendation

Olanzapine is indicated in the treatment of schizophrenia. Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Olanzapine is indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder.

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Olanzapine Apotex in the above mentioned indication was favourable and therefore recommended the granting of the marketing authorisation.