

SCIENTIFIC DISCUSSION

1. Introduction

Olanzapine Neopharma 2.5, 5, 7.5, 10 and 15 mg coated tablets is a generic medicinal product containing olanzapine as the active substance. The reference product Zyprexa 2.5, 5, 7.5, 10 and 15 mg coated tablet has been centrally authorised on 27/09/1996.

Olanzapine, a thienobenzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. They have greater affinity for serotonin 5-HT₂ serotonin receptors than for dopamine D₂ receptors and cause fewer extrapyramidal symptoms (EPS) in contrast with classical antipsychotics (e.g. 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 Neopharma is the same as for the authorized Reference medicinal product Zyprexa.

2 Quality aspects

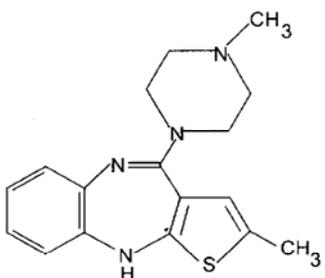
Introduction

Olanzapine Neopharma exists as 2.5, 5, 7.5, 10 and 15 mg coated tablets.

It contains olanzapine as the active substance. The excipients used are the following compendial excipients lactose monohydrate, maize starch, magnesium stearate, hydroxypropylcellulose and non-compendial ones for the coating (Opadry white and blue)

The primary packaging is made of Aluminium/Aluminium (Al/Al) blisters.

Active Substance



The active substance olanzapine (INN and chemical name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine) is a yellow crystalline powder. Physico-chemical properties have been adequately described including solubility and polymorphism. Olanzapine can exist as 5 possible polymorphic forms (I, II, III, IV and V). The control of polymorphism has been achieved and was found to be stable during stability studies. The structure has been fully elucidated by ¹H-NMR, UV, IR and mass spectroscopy, and elemental analysis. Physico-chemical characterisation includes appearance, solubility, loss on drying, tapped density, DSC scan and X-ray diffraction to identify polymorphic form. The active substance has no chiral centres and no isomerism could be found in the literature.

- **Manufacture**

The scientific information has been submitted as an Active Substance Master File (version August 2006). Olanzapine is obtained from one manufacturer via a 3 steps synthesis. The final product is dried, sifted and packed into food grade double PE bags kept in fibre drums.

- **Specification**

The applicant has provided an in-house monograph since olanzapine is not described in any pharmacopoeia. Satisfactory specification for olanzapine includes parameters such as appearance, solubility, identification (IR and UV), melting range, loss on drying, residue on ignition, heavy metals, chromatographic purity or related substances (HPLC), residual solvents (GC), particle size (laser diffraction), tapped density, polymorphism (DSC and XRPD), assay (HPLC). Analytical methods have been described and validated when non-compendial in accordance with ICH requirements.

Appropriate discussion has been presented on organic and inorganic impurities. Impurity levels have been provided for three batches of active substance manufactured by the proposed synthetic route. Results were found to be in accordance with ICH limits and individual impurities remained below the ICH qualification limits. Specification for residual solvents is in line with the Note for guidance ICH Q3C. Residual solvents data were below the ICH limits. There is no safety concern.

Certificates of analysis have been provided for three full scale batches. Results comply with the proposed specification and confirm the consistency of the process.

Olanzapine is packed in polyethylene bags made of food grade polymer complying with EC Directive 2002/72/EEC. Satisfactory specification, certificates of analysis and IR identification are presented for the packaging.

- **Stability**

Stability studies have been carried out on 10 batches (6 batches in the proposed packaging and 4 batches in the former one) under ICH conditions (up to 60 months at 25°C/60% RH, up to 24 months at 30°C/65%RH and 6 months at 40°C/75%) including forced degradation studies. The following parameters have been studied: description, polymorphic identity, identification, loss on drying, chromatographic purity, chemical and polymorphic assay.

Results showed no significant change and remained within the specification when olanzapine is stored in the proposed packaging material whereas out-of specification results were found in the former packaging. Therefore the proposed re-test period is justified based on the stability results when olanzapine is kept in the proposed packaging.

Medicinal Product

Olanzapine Neopharma exists as 2.5, 5, 7.5, 10 and 15 mg coated tablets. The excipients used in the formulation are lactose monohydrate and maize starch as filler and binder, hydroxypropylcellulose as a disintegrant agent, magnesium stearate as a lubricant. A coating has been used to differentiate the tablets. The qualitative and quantitative composition is detailed for the coating agents Opadry. The Olanzapine tablets are packed in Aluminium/Aluminium (Al/Al) blisters and cardboard cartons.

- **Pharmaceutical Development**

The objective was to obtain Olanzapine tablets achieving pharmaceutical equivalence and bioequivalence with the product of reference Zyprexa 2.5, 5, 7.5, 10 and 15 mg coated tablets.

Pharmaceutical development has been appropriately described, in particular the choice of particle size of olanzapine to obtain satisfactory dissolution properties. The control of the polymorphic form has been achieved during the synthesis of olanzapine.

Common compendial excipients have been chosen for Olanzapine tablets formulation except for the coating agents which have in-house specification. No novel or unusual excipients have been used. No compatibility issue could be identified between olanzapine and the excipients.

Adequate formulation development has been presented and the ratio between the excipients and the drug substance is identical for the five strengths.

Moreover, in order to demonstrate the equivalence of the Olanzapine Neopharma immediate release tablets and the reference product Zyprexa coated tablets: Comparative dissolution data between the proposed and reference products (all five strengths) have been provided including the biobatch and the batch of reference product bioequivalence study. In all cases dissolution is $\geq 85\%$ in 15 minutes and since the discriminatory power has been proven, the dissolution can be considered as similar. The dissolution method has been appropriately detailed including the choice of the method and the conditions.

Comparative impurity profiles have been presented between the reference product and the Olanzapine Neopharma product for the 5 strengths. All impurities were present at very low level, and the products can be concluded similar from the impurity point of view.

In vivo comparison has been made in bioequivalence study.

The following products were used: test product – Olanzapine 10 mg tablets and, reference product – Zyprexa 10 mg tablets.

The 10 mg tablets were chosen, because 2.5; 5.0; 7.5 and 10.0 mg have the same ratio between the active substance and excipients and the 15 mg tablets are dose proportional to the 10 mg tablets. The biowaivers have been applied. This is acceptable because all conditions of guideline CPMP/EWP/QWP/1401/98 have been fulfilled:

- the same manufacturing site and manufacturing process is used for all strengths
- pharmacokinetic is linear
- the qualitative components of different strengths are the same
- the composition of all strengths is proportional
- the dissolution profile is similar for all five strengths

Among the available options of tableting (direct compression, dry and wet granulation), the wet granulation was chosen since it was the preferred method for a low dose formulation and for a water insoluble active substance.

The process can be considered as standard. This has been supported by results during formulation development, by the successful scale-up and by the validation of the process itself.

The excipients used are Lactose monohydrate, maize starch, magnesium stearate and purified water (used for the manufacture only), hydroxypropylcellulose. They are controlled according to their relevant PhEur or USP monographs.

Two non-pharmacopeial coating agents Opadry II White and Opadry Blue have been tested according to appropriate in-house monographs. Details of their composition have been presented. The specifications are acceptable. All the components of the coating agents are Ph Eur quality except the dyes. This is acceptable.

Methods used for non-compendial excipients have been described but not validated since they are very simple, this is satisfactory. Compendial methods are accepted as such. Satisfactory Certificates of analysis of all excipients have been provided.

Magnesium stearate and lactose monohydrate are of animal origin. A satisfactory current copy of Certificate of Suitability from the PhEur and a BSE statement have been provided for magnesium stearate. The conformity with Note for Guidance EMEA/410/01 rev 2 has been confirmed.

The Al/Al blisters were chosen for packaging of Olanzapine tablets and the suitability of the packaging was confirmed by stability study.

- **Manufacturing of the product**

The manufacture of the finished product consists of a standard wet granulation process followed by compression and coating. Full description of the process has been provided and include details of operating conditions. Satisfactory in-process controls performed during the manufacture of Olanzapine tablets have been provided. No critical steps could be identified in the manufacturing process but uncoated tablets were classified as intermediate product. Appropriate controls have been performed on the uncoated tablets.

The process validation has been carried out on two pilot scale batches per strength and showed the process is adequately controlled and reproducible. A satisfactory validation plan has been presented

for the validation of the process on commercial batches, according to the Annex I to *Note for Guidance on Process Validation CPMP/848/96*.

- **Product specification**

Specifications at release and at the end of the shelf-life include description, tablet diameter, identification of olanzapine, identification of titanium dioxide, identification of the coating, uniformity of weight, average weight of the tablet, disintegration time, uniformity of content, uniformity of dosage units, dissolution, related substances, assay of olanzapine, microbiological quality.

The proposed specifications are acceptable in particular the skip-testing approach for microbiological quality. Release and shelf life limits for the assay of olanzapine are in line with batch and stability data. Limits for related substances comply with ICH guidelines Q3B and on the maximum daily dose - so the proposed limits are acceptable. No new impurities have been arising compared to the active substance and the specifications have been justified.

Analytical methods have been satisfactorily described and validated in accordance with ICH requirements except for PhEur methods.

Data have been presented for 2 pilot batches of each strength. All the results are in compliance with the proposed specification and demonstrate the consistency of the manufacture.

The packaging material is a blister strip made of 3 ply Al/Al film, packed in cardboard cartons. Satisfactory specifications for blisters have been provided as well IR identification and certificates of analysis. The packaging material complies with PhEur and EC Directive 2002/70/EC.

- **Stability of the product**

Stability studies have been carried out on 2 pilot batches of each strength kept in the commercial packaging under ICH conditions (up to 36 months under at 25°C / 60% RH, up to 12 months at 30°C / 65% RH, 6 months at 40°C / 75% RH). Parameters tested were description, disintegration, dissolution, assay, microbial limit test and related substances. Results remain within the specification under long-term and intermediate conditions. Based on the data, the proposed shelf-life can be granted under the precautions of storage stated in the SPC.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have 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.

3. Non-Clinical aspects

This application is being made under Article 10.1 of Directive 2001/83/EC. Pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well characterised. As olanzapine is widely used and well-known, non-clinical testing strategy did not include any further toxicological or pharmacological studies. Reference is made to the originator's data and to published literature. The active substance used in the reference product and the submitted generic application is identical, the excipients used in drug formulation are conventional, well known and broadly used in other medicinal products. Declared impurities in amounts present in the formulation do not require further identification and qualification. No further studies are required and the applicant has justified why no such data was provided.

4. Clinical Aspects

Introduction

The CHMP assessment addressed pharmacokinetic data in respect of bioequivalence studies.

GCP aspects

Clinical bioequivalence studies were performed in healthy volunteers. In these studies the compliance to regulatory, ethical and GCP requirements of clinical phases can be recognized. The clinical facility has recently been inspected by an EU inspection.

In accordance to Art 8 (ia) of the amended Directive, Art 9.4(c) and Art 127 (a) of the new Regulation, the Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Inspections were carried out during the assessment procedure: the inspection has not resulted in critical findings and the studies can be accepted in the context of a marketing authorization application.

Exemption

The Applicant submitted only one comparative bio-availability study with 10 mg tablets to determine whether Olanzapine 2.5 mg, 5.0 mg, 7.5 mg, 10.0 mg and 15.0 mg Tablets to be licensed by Neopharma Ltd. demonstrate equivalent pharmacokinetic characteristics to the Eli Lilly and Company brand Zyprexa 2.5 mg, 5.0 mg, 7.5 mg, 10.0mg and 15.0 mg Tablets. However, the Applicant adequately justified the lack of the bioequivalence studies for the other strengths according to the requirements of the Guideline CPMP/EWP/QWP/1401/98 section 5.4.

Clinical studies

To support the application, the Applicant has submitted a single bioequivalence study (study 007/05). The design of the study was an open label, balanced, randomized, analyst blind, two treatment, two period, two sequence, single dose, crossover oral bioequivalence study in 24 healthy male volunteers. The study was performed to determine whether Olanzapine 10 mg Tablets, which is the subject of this application, demonstrates equivalent pharmacokinetic characteristics to the Eli Lilly brand Zyprexa 10 mg Tablets (containing 10 mg Olanzapine).

Pharmacokinetics

- Methods

STUDY DESIGN

The study number 007/05 was an open label, balanced, randomized, analyst blind, two-treatment, two-period, two-sequence, crossover with oral single dose in 24 healthy male volunteers under fasting conditions.

The study was conducted using the facilities of a Contract Research Organisation located in Mumbai, India, and was carried out over the period 10/05/05 to 02/06/05.

After an overnight fast of at least 10 hours, the subjects were dosed between 08:00 and 08:21 a.m. A single oral dose (1 x 10 mg) was administered with 240 ml of water. A controlled meal was served about 4 hours post-dose, and fluids were not permitted for 1 hour before and 2 hours after dosing. The subjects were confined at least 11 hours before dosing and until after 24-hour blood sample was taken in each period. Blood samplings were performed pre-dosing and at different time-points up to 168 hours post-dose. Single doses of olanzapine were separated by a wash-out period of 2 weeks.

There was a small number of protocol deviations, including several missing blood samples. None of the deviations were considered to have any impact on the overall outcome of the trial. The deviations were presented appropriately and can be seen in the full study report.

The study was declared to be conducted in compliance with Good Clinical Practice, and this was verified and confirmed by an inspection. The centre was inspected by internal quality assurance department of the Clinical Research Organisation and the study protocol was approved by an independent Ethical committee.

TEST AND REFERENCE PRODUCTS

Olanzapine Neopharma 10 mg coated tablets by Neopharma Ltd. has been compared to Zyprexa 10 mg coated tablets by Eli Lilly Netherlands BV.

POPULATION(S) STUDIED

Twenty four healthy male subjects of mean age 24.2 years and mean body mass index 20.93 were enrolled in the study. All volunteers were Asian and light smokers (up to 6 cigarettes per day) were allowed to enter the study. All volunteers passed standard medical examination. Twenty three volunteers completed the study and were analyzed, one subject (number 24) did not performed Period 2 and was excluded from the final analysis.

ANALYTICAL METHODS

A validated HPLC method with MS/MS detection (LC-MS/MS) was used for plasma analysis.

PHARMACOKINETIC VARIABLES

The primary pharmacokinetic parameters according to protocol were the area under the plasma concentration curve from administration to last observed concentration at time t (AUC_{0-t}), AUC extrapolated to infinity (AUC_{0-inf}) and maximal plasma concentration (C_{max}). Secondary variables were determined as time of the C_{max} – T_{max} , terminal half-life – $T_{1/2}$ and elimination rate constant – K_{el} . WinNonlin software and SAS software release 9.1 were used for analysis.

STATISTICAL METHODS

The statistical analysis consisted of an ANOVA, performed on untransformed and log-transformed data. 90% confidence intervals for the ratio of means between drug formulations were calculated for the log-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} . The acceptance range was pre-defined within 85–125%. The statistical model included sequence, period and treatment as factors for the subsequent ANOVA analysis.

- Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm 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	335.31 \pm 239.93	777.72 \pm 253.46	21.18 \pm 6.43	5.62 \pm 2.19	29.73 \pm 8.35
Reference	715.08 \pm 173.81	744.23 \pm 172.89	20.37 \pm 5.07	6.72 \pm 2.27	30.82 \pm 6.62
*Ratio (90% CI)	93.71 – 108.64	95.15 – 110.14	96.90 – 108.80	N.A.	N.A.
Intra-subject CV (%)	14.63	14.48	11.44	N.A.	N.A.

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
 $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
 C_{max} maximum plasma concentration
 T_{max} time for maximum concentration
 $T_{1/2}$ half-life

*ln-transformed values

The mean ratios of the AUC_{0-t} , AUC_{0-inf} , and C_{max} for olanzapine were within the acceptable confidence intervals of 80–125%. Bioequivalence was assessed according to the standard equations. The pharmacokinetic parameters reported in the study are consistent with literature reports. The

individual data listings as well as linear and semilogarithmic individual graphs are presented in the dossier.

A statistically significant effect was not detected. Both treatments were well tolerated after a single dose, with 14 non-serious adverse events reported in the study. The adverse events include drowsiness (9 subjects), dizziness (2 subjects), pain in calf muscle (1 subject) and giddiness (1 subject). These adverse events were randomly distributed between the test and reference product, except for the pain in the calf muscle, which was classified as probably related to the medication and is described in the SPC of both the reference and the test products.

- **Conclusions on clinical studies**

The BE study was designed and conducted according to the typical randomized cross-over design. All the primary parameters are well within the limit of 80-125 % for 90 % confidence intervals. The presented results of the means of AUC_{0-inf} and AUC_{0-t} with relatively low intraindividual variability indicate residual AUC area to be less than 5%.

All the clinical work was declared to be in compliance with GCP, and this was verified and confirmed by an inspection.

Based on the presented study Neopharma Olanzapine is considered bioequivalent with Zyprexa by Eli Lilly. The results of study 007/05 with 10 mg formulation can be extrapolated to the other strengths (2.5 mg, 5.0 mg, 7.5 mg and 15.0 mg) submitted for the marketing authorisation, according to the conditions in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamics

No studies were submitted.

Additional data

Comparative dissolution data between the proposed and reference products (all five strengths) have been provided including the biobatch and the batch of the reference product used in the bioequivalence study. In all cases the dissolution was comparable.

Discussion on Clinical aspects

The efficacy, safety and clinical pharmacology of the active ingredient olanzapine are already well-established and documented for the original medicinal product Zyprexa. The submitted bioequivalence study is designed and reported in accordance with the relevant EU note for guidance. The data of this study sufficiently demonstrate that the tested formulation intended for marketing is bioequivalent to the innovator product. The bioequivalence demonstrated for tablets of the strength 10mg may be extrapolated also to strengths 2.5, 5, 7.5 and 15 mg. The validity of the BE data was confirmed following the positive outcome of a GCP inspection conducted at the clinical and analytical sites.

Post marketing experience

No post-marketing data are available. Olanzapine Neopharma has not been marketed in any country.

5. Pharmacovigilance

Pharmacovigilance System

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product.

- **PSUR**

The PSUR submission schedule for Olanzapine Neopharma should follow the PSUR submission schedule for the reference medicinal product.

- **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 minimisation activities have been identified, a Risk Management Plan was not required.

- **User consultation**

The results of user consultation provided indicates 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 in patients /users are able to act upon the information that it contains.

6. Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality and non 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

Based on the CHMP review of available data, the CHMP considered by consensus decision that the risk-benefit balance of Olanzapine Neopharma in the treatment of schizophrenia was favourable and therefore recommended the granting of the marketing authorisation.

Medicinal product no longer authorised