European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/507381/2008

ASSESSMENT REPORT

FOR

OLANZAPINE MYLAN

International non-proprietary Name

OLANZAPINE

Procefure No. (EMEA/H/C/961)

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Generics [UK] Ltd. submitted on 30 November 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Olanzapine Mylan, 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 application legal basis refers to Article 10(1) at the time of the opinion.

The chosen reference product is:

■ Reference medicinal product which is or has been authorised in accordance with the community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Zyprexa 2.5/5/7.5/10/15/20 mg Coated Tablets
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- First authorisation: 27/09/96
- Member State (EEA)/Community: EU registration

■ Reference medicinal product authorised in the Community/Member State where the application is made:
- Product name, strength, pharmaceutical form: Zyprexa 2.5/5/7.5/10/15/20 mg Coated Tablets
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Marketing authorisation number(s): EU/1/96/022

■ Medicinal Product used for bioequivalence study (where applicable)
- Product name, strength, pharmaceutical form: Zyprexa, 10 mg and 15 mg Coated Tablets
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Member State of source: UK

Rapporteur :	Dr. Broich
Pharmacovigilance Rapporteur :	Dr. Laitinen-Parkkonen

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 30 November 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008.
- During the meeting on 21-24 April 2008 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 25 April 2008.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2008.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 04 July 2008.
- During the meeting on 21-24 July 2008 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 Mylan.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Olanzapine Mylan 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg Film-coated tablets is a generic medicinal product containing olanzapine as the active substance. The reference product Zyprexa 2.5, 5, 7.5, 10, 15 and 20 mg coated tablet has been centrally authorised on 27 September 1996.

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 then for dopamine D_2 receptors and cause fewer extrapyramidal symptoms (EPS) and improve negative symptoms in contrast to 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 Mylan is the same as for the authorized Reference medicinal product Zyprexa.

Before the adoption of the opinion the Applicant decided to change the name of the medicinal product from Olanzapine Merck Generics to Olanzapine Mylan and this was endorsed by the CHMP and the Name Review Group.

2.2 Quality aspects

Introduction

Olanzapine Mylan is presented as film-coated tablets containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg of olanzapine as active substance. The other ingredients are lactose monohydrate, maize starch, pregelatinised maize starch, crospovidone and magnesium stearate.
The film consists of polyvinyl alcohol, titanium dioxide, talc, lecithin soya and xanthan gum. The film-coated tablets are marketed in aluminium/aluminium blisters packed in cartons or in polypropylene tablet containers with polyethylene caps.

Drug Substance

The drug substance is olanzapine and its chemical name is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine according to the IUPAC nomenclature.
Olanzapine is pale yellow to yellow crystalline powder. Olanzapine shows polymorphism. However, only one form will be used in this medicinal product. Olanzapine is freely soluble in chloroform and sparingly soluble in acetic acid. The above-mentioned active substance does not contain chiral centres and therefore, does not exhibit stereoisomerism.

- **Manufacture**

Olanzapine is synthesised in three reactions steps. The manufacturing process has been adequately described in an 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. The purified active substance is finally packed in primary bag of transparent polythene closed with a plastic tag. The primary bag is placed in a secondary opaque polythene bag tied using a plastic tag.
Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy and mass spectroscopy. The molecular weight was determined by elemental analysis. The polymorphic form was confirmed by X-ray powder diffraction.

- **Specification**

The active substance specifications include tests for appearance (yellow crystalline powder) solubility, identification (IR/XRD), loss on drying, residue on ignition, heavy metals, Impurities (HPLC), residual solvents (GC), assay (HPLC), and particle size.
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, intermediate and accelerated studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: description, identification by IR and XRD, loss on drying, chromatographic purity by HPLC and assay on dried basis by HPLC. It is important to underline that the test methods applied are those used for release of the drug substance. It was noticed that no tendencies for increases in impurities were seen during storage. Furthermore stress studies were also performed under UV, water, oxidation, acid, base, thermal and light conditions.
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.

Drug Product

- **Pharmaceutical Development**

All information regarding the choice of the drug 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 to develop generic tablets that had immediate release properties. It was concluded that in order to achieve a rapid and complete dissolution of the medicinal product, the active substance would need to be fine and therefore the particle size of the active substance is suitably controlled. A wet granulation process was considered the most appropriate in order to avoid segregation during manufacturing. Nevertheless, direct compression process was attempted**,** but the results confirmed that wet granulation was the best option.
Pilot batches of all tablet strengths were manufactured in order to optimise the formulation via a wet granulation method.
Data presented for the physical characteristics of the generic tablets and the originator Zyprexa tablets show that they are similar in physical appearance. Comparative dissolution profiles in 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.
All the excipients used are well known and commonly used in the pharmaceutical industry. Statements from the suppliers of lactose and magnesium stearate on the risk of BSE/TSE were provided and found to be acceptable.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, blending, wet granulation, compressing and coating.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps in the manufacturing process.

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

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, uniformity of weight (BP), average tablet weight, identification, thickness, hardness, disintegration (Ph Eur), dissolution, uniformity of dosage units (Ph Eur), impurities (HPLC), assay and microbial limits (Ph Eur).
It was verified that no new impurities have been arising compared to the active substance and the specifications have been justified
All analytical procedures that were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis data for two pilot scale batches of each strength confirm that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the finished product.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Two pilot scale batches of each strength have been stored at long term, intermediate and accelerated conditions. It was verified that the following parameters were controlled: appearance, average tablet weight, identification, thickness, hardness, disintegration, dissolution, chromatographic purity, assay and microbial purity.
One production batch per strength was examined for photostability at ICH conditions and the results obtained justify, that no labelled storage condition concerning exposure to light is required.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological 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) and this is confirmed by in-vivo bioequivalence results (see the clinical part of the report). At the time of the CHMP opinion, there were no unresolved quality issues. Therefore, 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 being made under Article 10.1 of Directive 2001/83/EC.
Olanzapine Mylan film-coated tablet is a generic medicinal product, having the same qualitative and quantitative composition in active substance (olanzapine) and the same pharmaceutical form as the reference medicinal product Zyprexa. Pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well characterised. 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 additional safety studies. No further studies are required and the applicant has justified why no such data was provided.

2.4 Clinical Aspects

Introduction

The Applicant addressed pharmacokinetic data in respect of bioequivalence studies. Two single dose bioequivalence studies, one with the 10 mg film-coated tablets (Study BS590) and one with the 15 mg film-coated tablets (Study BS591) were submitted to support this application.

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.
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.

Exemption

The applicant submitted a marketing authorisation application for 6 different strengths (i.e. 2.5, 5, 7.5, 10, 15 and 20mg) of the film-coated tablets, for which only two bioequivalence studies in the strengths 10 mg and 15 mg were provided.
However, the requirements indicated in chapter 5.4 of the Guideline CPMP/EWP/QWP/1401/98 "NfG on the Investigation of Bioavailability and Bioequivalence" were fulfilled. As a result, the extrapolation of the results of the 10 mg Olanzapine Mylan film-coated tablet to the 2.5, 5, 7.5 tablets and the extrapolation of the results of the 15 mg Olanzapine Mylan film-coated to the 20 mg tablet was justified.

Clinical studies
This application refers to the immediate release tablet olanzapine 2.5, 5, 7.5, 10, 15, 20 mg.
To support this application the applicant has submitted the following two bioequivalence studies:
Study BS590 was a randomised, open-label, 2- way crossover, bioequivalence study of Olanzapine 10 mg tablet and Zyprexa (reference) following a 10 mg dose in healthy subjects under fasting conditions.
Study BS591 was a randomised, open-label, 2- way crossover, bioequivalence study of Olanzapine 15 mg tablet and Zyprexa (reference) following a 15 mg dose in healthy subjects under fasting conditions.
The objective of these studies was to compare the rate and extent of absorption of olanzapine from Generics [UK] Ltd (United Kingdom) and Eli Lilly Nederland BV (The Netherlands) Zyprexa, administered as a 1 x 10 and 1 x 15 mg tablet respectively, under fasting conditions.

Pharmacokinetics

- Methods

STUDY DESIGN
The study number BS590 was a randomised, open-label, 2- way crossover, bioequivalence study of Olanzapine 10 mg tablet and Zyprexa (reference) following a 10 mg dose in healthy subjects under fasting conditions. The study took place at a Contract Research Organisation in Quebec, Canada and was carried out over the period 2007-05-14 to 2007-06-11.

In each period subjects were housed at the Clinical Research Facility from at least 10 hours prior to the drug administration until after 72 hour post dose draw, in each period. The treatment phases were separated by a wash out period of 21 days.
All included susbjects received a single oral dose of 1 x 10 mg tablet in each study period.

During each study period, blood samples were taken pre-dose and at different time-points up to 168 hours after drug administration. Plasma was harvested from these samples and assayed for olanzapine using a validated HPLC method.

TEST AND REFERENCE PRODUCTS
Test (A): Olanzapine, 10 mg, Company Responsible for Marketing: Generics [UK] Ltd.
Reference (B): Olanzapine (Zyprexa.), 10 mg, Company Responsible for Marketing: UK Eli Lilly Nederland BV, The Netherlands.

POPULATION(S) STUDIED

Twenty-two healthy adult subjects (12 males and 10 females) aged between 22 and 53 years (mean 40 ± 10), with a body mass index (BMI) between 20.8 and 29.5 (mean 25.7 ± 3.2) and a weight range of 52.2 to 105.5kg (mean 75 ± 14.1) participated in the study. Twenty subjects were Caucasian and 2 were American Hispanic. All female subjects were taking adequatecontraceptive precautions.

ANALYTICAL METHODS

The plasma samples were analyzed by LC/MS-MS method for detection of olanzapine.
The method has been validated with respect to specificity, sensitivity, between-batch and within-batch accuracy and precision and linearity.

PHARMACOKINETIC VARIABLES

The following pharmacokinetic parameters were calculated in this study: $AUC_{0\text{-}t,}$ $AUC0_{inf}$, C_{max}, $C_{max}/AUC_{0\text{-}t}$, $T_{1/2\ el}$, T_{max}, Residual area and K_{el}.
Pharmacokinetic parameters for plasma olanzapine were calculated as follows:
$AUC_{0\text{-}t}$: The area under the plasma concentration versus time curve from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUC_{inf}: The area under the plasma concentration versus time curve from time 0 to infinity. AUC_{inf} was calculated as the sum of the $AUC_{0\text{-}t}$ plus the ratio of the last measurable plasma concentration to the elimination rate constant.
C_{max}: Maximum measured plasma concentration over the time span specified.
t_{max}: Time of the maximum measured plasma concentration.

STATISTICAL METHODS

Pharmacokinetic parameters and plasma concentrations were summarized by treatment.
The 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated for ln-transformed C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ by ANOVA.
Bioequivalence was declared when the 90% CI of the ratio of the means (Test/Reference) for olanzapine AUC and C_{max} was within 80-125% range. Furthermore it was examined non-parametric test (Wilcoxon) and 90% non-parametric CI calculated for T_{max}; inter- and intra-subject coefficient of variation (ISCV%); and power values calculated for Cmax and $AUC_{0\text{-}t}$.
SAS (release 8.02) and other software were used to calculate the pharmacokinetic parameters and perform non-compartmental analyses of pharmacokinetic parameters and statistical analyses.
Adverse events, vitals signs measurements, and standard laboratory evaluations were evaluated descriptively only.

- Results

There were no drop-outs from the study, so that all 22 subjects were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters of olanzapine (non-transformed values; arithmetic mean ± SD, t_{max} $T_{1/2}$ mean)

Treatment	$AUC_{0\text{-}t}$ pg/ml/h	$AUC_{0\text{-}\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h	$T_{1/2}$ h
Test	520469.59 ±145486.04	560410.94 ±168364.79	11951.77 ±3194.70	5.89 ±2.08	44.59 ±8.42
Reference	506708.91 ±139313.10	543838.11 ±154447.93	11666.10 ±3028.43	5.51 ±1.90	43.50 ±7.34
***Ratio (90% CI)**	99.36 % to 105.67 %		96.43 % to 108.24 %		
Intra-subject CV (%)	5.92 %		11.14 %		

$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	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*

Plasma concentration-time curves of each subject (linear-linear and log/linear scale) are presented.
The mean extrapolated AUC is below 20% for all subjects and treatments (Residual area mean Reference: 6.53, Test: 6.60).

There was no detectable pre-dose concentration at any of the study periods. ANOVA for olanzapine showed no significant effect of period or treatment on all primary parameters.

Secondary pharmacokinetic parameters: For T_{max} and $t_{1/2}$ no statistically significant differences were found between the two formulations.

Protocol deviations
Three deviations from study protocol requirements have been registered.

1. Storage of the study medication; the humidity of the facility storage fell beneath the acceptance range (to 25.77%RH) from 13 May 2007 until 15 May 2007.
2. Subject no 15 walked for approximately 2 minutes
3. Subject no 9 the post dose blood sample in period 1 was not filled enough, so it could not be analysed.

Furthermore some blood draw time deviations occurred; these times were adjusted in the data sets to reflect the actual times at which the samples were obtained.

Adverse events
No serious adverse events occurred during the conduct of the study. Safety data have been evaluated on 22 subjects for the Test formulation and on 22 subjects of the Reference formulation. A total of 99 adverse events occurred 56 reported by 22 subjects who received treatment A and 43 of the 22 subjects who received treatment B. The most commonly reported adverse event was “Somnolence”. 34 of the 99 adverse events were graded as mild and 65 as moderate.

Study BS591:

Methods

Study design
The study number BS591 was a randomised, open-label, 2- way crossover, bioequivalence study of Olanzapine 15 mg tablet and Zyprexa (reference) following a 15 mg dose in healthy subjects under fasting conditions..The study took place at a Contract Research Organisation in Quebec, Canada and was carried out over the period 2007-06-11 to 2007-07-09.

In each period subjects were housed at the Clinical Research Facility from at least 10 hours prior to the drug administration until after 72 hour post dose draw, in each period. The treatment phases were separated by a wash out period of 21 days.
All included susbjects received a single oral dose of 1 x 15 mg tablet in each study period.

During each study period, blood samples were taken pre-dose and at different time-points up to 168 hours after drug administration.

Test and reference products
Test (A): Olanzapine, 15 mg, Company Responsible for Marketing: Generics [UK] Ltd
Reference (B): Olanzapine (Zyprexa.), 15 mg, Company Responsible for Marketing: Eli Lilly Nederland BV, The Netherlands

Population(s) studied
Twenty-one healthy adult subjects (14 males and 7 females) aged between 21 and 55 years (mean 38 ±10), with a body mass index (BMI) of between 21 and 29.6 (mean 25.8 ± 2.9) and a weight range of 57.3 to 97.9 kg (mean 74.2 ±9.5) participated in the study. Twenty subjects were Caucasian and 1 was Black. All female subjects were taking adequate contraceptive precautions.

Analytical methods
The plasma samples were analyzed by LC/MS-MS method for detection of olanzapine.
The method has been validated with respect to specificity, sensitivity, between-batch and within-batch accuracy and precision and linearity.

Pharmacokinetic Variables and Statistical methods
The pharmacokinetic variables examined and statistical methods correspond to study 1.

Results
17 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters of olanzapine (non-transformed values; arithmetic mean ± SD, t_{max} $T_{1/2}$ mean)

Treatment	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h	$T_{1/2}$ h
Test	709475.54 ±215059.95	745718.16 ±237607.71	16492.51 ±4835.77	6.29 ±2.65	36.95 ±6.44
Reference	714312.42 ±216304.70	748699.55 ±239449.78	17614.75 ±5302.99	4.95 ±1.89	36.71 ± 6.36
***Ratio (90% CI)**	94.65 % to 103.58 %		88.43 % to 99.33 %		
Intra-subject CV (%)	7.50		9.67		

$AUC_{0-\infty}$	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*

Plasma concentration-time curves of each subject (linear-linear and log/linear scale) are presented.
The mean extrapolated AUC is below 20% for all subjects and treatments (Residual area mean Reference: 4.09 Test:4.43).

No statistical significant period effect was detected for AUC_{0-t}, AUC_{0-inf} and C_{max}.

The 0.00 sample (pre-dose concentration) of subject no. 17 was analysed three times and in all cases it showed an unacceptable internal standard response. Ultimately, the pre-dose concentration of subject no.17 was not reportable (NRV). Apart from this missing value there was no detectable pre-dose concentration at any of the study periods.

For subject no 8 several values could not be reported. Because these missing values the characterization of the pharmacokinetic parameters may be non robust. Therefore an additional statistical analysis without subject no 8 was performed. If the data of subject no 8 are excluded from the analysis the 90% CI for olanzapine AUC and C_{max} still are within the accepted range.

Protocol deviations
4 subjects withdrew from the study. Two subjects withdrew due to adverse events (vomiting subject 3 and fainting intermittent subject 7. The other two subjects (no 5 and 12) withdrew due to personal reasons.
Seven deviations from the study protocol requirements have been registered; post-study procedures (vital signs) were performed 17 days too late, documentation of exclusion criteria was missing at the beginning of the study but they were answered at the end of the study, consumation of coffee of one subject, only 21 subjects instead of 22 received the study medication, the question whether the subjects consumed pomelo products within 7 days prior to the study drug was not asked.

Adverse events
92 post-dose adverse events were reported by 20 of the 21 subjects received at least one of the study medication. 52 adverse events reported by 18 of the 20 subjects who received treatment. A and 40 adverse events reported by 16 of the 19 subjects who received treatment B. The most commonly reported adverse event was "Somnolence". All adverse events were not serious and recover before the end of the study.

Additional data
***In vitro* dissolution profiles**
Dissolution comparisons of products used in the BE studies are included in this application and are used to support the exemption for studies in each of the submitted strengths of the product.

Dissolution rates of olanzapine from Olanzapine Mylan tablets and ZYPREXA tablets were determined. Different dissolution media were used, i.e. 0.1 M Hydrochloric acid, Acetate buffer solution pH 4.5 and Phosphate buffer solution pH 6.5.

In all investigated media the dissolution of olanzapine from Olanzapine Mylan tablets in all strengths was fast and complete. The *in vitro* dissolution of olanzapine of Olanzapine Mylan tablets is faster than the dissolution of Zyprexa.

2.5 Pharmacovigilance

- **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.

- **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.

- **PSUR**

The PSUR submission schedule for Olanzapine Mylan tablets should follow the PSURs submission schedule for the reference product Zyprexa.

- **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.

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 studies were 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 and 15mg may be extrapolated also to strengths 2.5, 5, 7.5 and 20 mg.

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 Mylan in the above mentioned indication was favourable and therefore recommended the granting of the marketing authorisation.