# SCIENTIFIC DISCUSSION

## 1. Introduction

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

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 Teva is the same as authorized for the Reference medicinal product Zyprexa.

## 2. Quality aspects

### Introduction

Olanzapine Teva is presented in the form of film coated tablets and orodispersible tablets.

The film coated tablets contain 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg of olanzapine as active substance. Other ingredients are:
Tablet core: lactose monohydrate, hydroxypropylcellulose, crospovidone type A, silica colloidal anhydrous, microcrystalline cellulose and magnesium stearate
Tablet coating: hypromellose and colorants.

The orodispersible tablets contain 5 mg, 10 mg, 15 mg, and 20 mg of olanzapine as active substance. Other ingredients are mannitol, sodium starch glycolate type A, D-glucose, vanilla flavouring and colorants.

Tablets and orodispersible tablets are sealed into blisters made of cold formed OPA/Al/PVC film and sealing aluminium foil.

### Active Substance

Olanzapine which has the chemical name 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b]-[1,5]benzodiazepine is a is a yellow or off-white crystalline solid which is not hygroscopic. Polymorphism has been observed for olanzapine.

- Manufacture

Olanzapine is prepared by synthesis and subsequent crystallization processes. The synthesis is described in an Active Substance Master File.
Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- Specification


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The active substance specification includes tests for description, identification (HPLC, IR), water content (KF), sulphated ash (Ph Eur), heavy metals (Ph Eur), purity (HPLC), assay (HPLC), residual solvents (GC), polymorphic form (XRD).
The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance. Impurities have been qualified and found to be acceptable from the point of view of safety

Batch analysis data of 3 batches of active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

Four batches of olanzapine synthesized according to the defined synthetic process were placed under ICH storage conditions (2-8 ºC up to 18 months and 25ºC/60%RH up to 6 months) in double aluminium laminated bags in HPDE containers. The parameters tested are description, identification (HPLC), polymorphic form (XRD), water, related substances, and assay.
Stress testing was also performed on one batch and included acid, base, oxidative, heat and light stress conditions.
The proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

**Finished Product**

Film coated tablets

- Pharmaceutical Development

The aim of the development was to obtain immediate release tablets containing qualitatively and quantitatively the same drug substance as the innovator product, and exhibit the same bioavailability. Dissolution tests were used as discriminating tests in order to select suitable formulations for further study. The development was performed first on the 20 mg strength. The other tablet formulations were derived from this strength.

The bioequivalence study was performed with the 10 mg strength. The excipients percentage composition is similar for all strengths, the only difference is the colouring agent. The bioequivalence study performed can be extrapolated to the other strengths according to the “Note for Guidance on Bioavailability and Bioequivalence”.

The excipients used are lactose monohydrate, hydroxypropylcellulose, crospovidone, silica colloidal anhydrous, microcrystalline cellulose and magnesium stearate. The colourants used are: Titanium dioxide (E171), Indigo carmine lake (E132) and Iron oxide (E172).
All the excipients are well known and commonly used in the pharmaceutical industry. Statements of the suppliers of lactose on the risk of BSE/TSE were provided.

Olanzapine Teva film-coated tablets are packaged in oriented polyamide (OPA) / Aluminium / Polyvinylchloride (PVC) cold formable foil – aluminium foil blisters.
The components of the OPA/Alu/PVC films comply with Directive 2002/72/AC as amended. The suitability of the packaging system was determined in the stability studies.

- Manufacture of the Product

The manufacturing process includes blending, granulation, tabletting, coating and packaging.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process.
The batch analysis datashow that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.


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- Product Specification

The product specifications include tests by validated methods for description, identification (HPLC, TLC), identification of titanium dioxide, indigocarmine, and iron oxide, content uniformity (HPLC), dissolution (Ph Eur), assay (HPLC), impurities/degradation products (HPLC), microbial limit test (Ph Eur).

Degradation products have been evaluated and found to be acceptable from the point of view of safety.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.
Batch analysis data submitted for all strengths confirm satisfactory uniformity of the product at release.

- Stability of the Product

Batches of 2.5 (2 batches), 5 (1 batch), 7.5 (1 batch), 10 (2 bathes), 15 (1 batch) and 20 (2 batches) mg film coated tablets packed in intended market containers were placed on stability under ICH conditions (25º C/60% RH, 30º C/65% RH) for 12 months and 40º C/75% RH for 6 months.
Photostability study was performed on one batch of 2.5 and 5 mg tablets stored according to Note of Guidance on photostability test.
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

<u>Orodispersible tablets</u>

- Pharmaceutical Development

The aim of the development was to obtain orodispersible tablets containing qualitatively and quantitatively the same active substance as the innovator product, and exhibiting the same bioavailability. The dissolution tests were used as discriminating tests in order to select suitable formulation. The development was performed first on the 20 mg tablets. The other tablet formulations were derived from the 20 mg tablets. Several excipient composition and disintegrant agents were tried. Percentage composition is essentially similar for all strengths. Development included the following characteristics: dissolving time in the mouth, mouth feel, taste, hardness and appearance of the tablet.

Bioequivalence studies were performed for the 10 mg strength and the 20 mg strength. Considering that all strengths have the same weight composition and identical or similar excipient composition, the results of the bioequivalence study may be extrapolated to other strengths, according to the *Note for Guidance on Bioavailability and Bioequivalence* .

The excipients used are mannitol, sodium starch glycolate type A, D-glucose and flavouring. The colourants used are: sunset yellow lake (E110), allura red lake (E129), indigo carmine lake (E132), tartrazine lake (E102), and erythrosine lake (E127). All the excipients are well known and commonly used in the pharmaceutical industry. Mannitol and, sodium starch glycolate are of Ph.Eur. quality. Flavour agent and all colourants are tested according to in-house specifications. Certificates of analysis of all excipients were provided. The flavouring ingredients comply with Directive 88/388/EEC.

The orodispersible tablets will be packaged in OPA / Aluminium / PVC cold formable foil – Aluminium peel off blisters. The components of the OPA/Alu/PVC films and the polyester part of the peel-off aluminium foil comply with Directive 2002/72/AC as amended.

- Manufacture of the Product


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The manufacturing process includes blending, granulation, tabletting, drying, bulk packaging, and packaging.
The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process.
The batch analysis data show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The product specifications include tests by validated methods for description, identification of olanzapine (HPLC, TLC), identification of colorants, content uniformity (HPLC), water content (KF), residual solvents (GC), disintegration (Ph Eur), assay (HPLC), impurities/degradation products (HPLC), microbial limit (Ph Eur).
Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.
The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.
Batch analysis data of two batches for all strengths except 5 mg (three batches) submitted confirm satisfactory uniformity of the product at release.

- Stability of the Product

Three batches of 5 mg tablets and 2 batches of 10, 15 and 20 mg tablets packed in the intended market containers and in bulk were placed on stability under ICH conditions (25º C/60% RH, 30º C/65% RH and 40º C/75% RH). The batches were tested for appearance, disintegration, assay, dissolution, related substances, total related substances, water, hardness, and microbiological purity.
Photostability study was performed on one batch of 2.5 mg tablets stored according to Note of Guidance on photostability test..

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 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. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

## 3. Non-Clinical aspects

The legal basis of this application is Article 10(1) of Directive 2001/83/EC as amended at the time of the opinion.

Olanzapine Teva film-coated and orodispersible tablets have the same qualitative and quantitative composition in active substance (olanzapine) and the same pharmaceutical forms as their respective reference products Zyprexa and Zyprexa Velotab. Pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well characterised. The excipients used in the drug formulation are conventional, well known and broadly used in other medicinal products. Declared impurities in amounts present in both formulations do not require additional safety studies. No further studies are required and the applicant has justified why no such data was provided. The overview was based on literature review, and this was considered appropriate. It is expected that the generic product Olanzapine TEVA will not affect the environmental load already known for olanzapine. As a result, an Environmental Risk Assessment is deemed not necessary.


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## 4. Clinical Aspects

**Introduction**
The rapporteur's assessment addressed pharmacokinetic data in respect of bioequivalence studies. Three single dose bioequivalence studies (Study 2006-1152, Study B0507 and Study A37552) were submitted to support this application.

**GCP aspects**
The clinical bioequivalence studies were performed at three different clinical research organisations. GCP and GLP aspects were provided.

**Exemption**
Film-coated tablets:
The 5, 7.5, 15, and the 20 mg tablets are dose-proportional with the 10 mg tablet. The 2.5 mg tablet have a similar composition in terms of excipients as compared to the 5 mg tablet. The tablets were manufactured by the same manufacturing process. Dissolution tests at pH 1, 4.5 and 6.8 showed comparable dissolution. In addition, olanzapine showed linear pharmacokinetics. Therefore the results obtained for the 10 mg tablet were extrapolated to the 2.5, 5, 7.5, 15 and 20 mg tablets.

Orodispersible tablets:
The 5 and the 15 mg orodispersible tablets have a similar excipients composition compared to the 10 and 20 mg orodispersible tablets.The tablets were manufactured by the same manufacturing process. Dissolution tests at pH 1, 4.5 and 6.8 showed comparable dissolution. In addition, olanzapine showed linear pharmacokinetics. Therefore the results obtained for the 10 and 20 mg orodispersible tablets were extrapolated to the 5, and 15 mg tablets.

Extrapolation of the results obtained for the 10 mg film-coated tablet to the other strengths was acceptable. The bioequivalence testing carried out on the 10 mg orodispersible tablet can be extrapolated to the 5 mg tablet. The bioequivalence testing carried out on the 10mg and 20 mg orodispersible tablets can be extrapolated to the 15 mg strength as the 10 and 20 mg strength encompass the 15 mg strength.
Extrapolation of the results obtained for the 10 and 20 mg orodispersible tablets to the other strengths was also acceptable.

**Clinical studies**
To support the application, the applicant has submitted 3 single dose bioequivalence studies, one with the 10 mg film-coated tablets, one with the 10 mg orodispersible tablets, and one with the 20 mg orodispersible tablets: Study 2006-1152 (10 mg film-coated tablet) which was a single-dose, 2-way cross-over study; Study B0507 (10 mg orodispersible tablet) which was a single-dose, 2-way cross-over study; Study A37552 (20 mg orodispersible tablet) which was a single-dose, 3-way cross-over study.

**Pharmacokinetics**

**Study 2006-1152 (10 mg film coated tablet):**

a) Methods

(1) STUDY DESIGN

This was a single-dose, 2-way cross-over study. Twenty-five non-smokers healthy subjects, 21 males and 4 females, aged 21 - 53 years, were included in this study. Each subject received a single dose (1 x 10 mg tablet) of both the test and reference olanzapine formulations. The tablets were administered in solid form with 240 ml water after overnight fasting. Fasting was continued for 4 hrs after dosing. For each subject there were 2 dosing periods, separated by a washout period of 14 days. Blood samples were taken pre-dose and up to 144 hours post administration.

(2) TEST AND REFERENCE PRODUCTS

Olanzapine 10 mg tablets (Teva, Hungary) were compared to Zyprexa 10 mg tablets.


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(3) POPULATION(S) STUDIED

Twenty-eight subjects were to be included in this study, however three subjects were not qualified to start the study. Twenty-five healthy subjects, twenty-one males and four females, aged 21 - 53 years, all non-smokers, were thus included in this study. All subjects completed the study entirely, and were included in the analysis.

(4) ANALYTICAL METHODS

Plasma samples were analysed using LC-MS/MS. The method was properly validated and a validation report was provided.. The results of the method validation and the bio-analytical analysis were in line with each other.

(5) PHARMACOKINETIC VARIABLES

Olanzapine $AUC_{(0\text{-inf.})}$ and $AUC_{(0\text{-t})}$ were calculated by linear trapezoidal method. $C_{max}$ and $t_{max}$, were derived directly from concentration-time-curve. Elimination rate constant was estimated from the slope of the regression line using the terminal data points of the semi-logarithmic plasma concentration - time curve. $T_{½}$ was calculated as $0.693/k_{el}$.

(6) STATISTICAL METHODS

The 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated for natural logarithm-transformed $C_{max}$, $AUC_{(0\text{-t})}$, and $AUC_{(0\text{-inf})}$ by ANOVA. Treatment, period, sequence, and subjects within sequence were included into the 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.

The $AUC_{0\text{-inf,}}$ $AUC_{o\text{-t}}$, and $C_{max}$ of test and reference were also tested for bioequivalence by the assessor using a different system. The least square means and the 90% CI of the (test/reference) ratios were calculated by ANOVA GLM procedure with period, treatment (test or reference) and subject within sequence as independent variables. The values were logarithmically transformed before ANOVA analysis.

- Results

The pharmacokinetic variables of olanzapine of the test and reference product are shown in Table 1. All pre-dose samples were zero in period 1, but in period 2, five subjects had pre-dose olanzapine concentrations of less than 0.2 ng/ml, which was less than 1.5% of the maximal plasma concentration.

**Table 1**. Pharmacokinetic variables of olanzapine of the test and reference (as mean ± s.d.; $t_{max}$ as median (range)).

| n=25 | Olanzapine Teva 10 mg tablet dose 10 mg Test | Zyprexa® 10 mg tablet dose 10 mg Reference |
|---|---|---|
| $AUC_{(0\text{-t})}$ (ng.h/ml) | 548 ± 153 | 551 ± 182 |
| $AUC_{(0\text{-inf})}$ (ng.h/ml) | 596 ± 170 | 612 ± 205 |
| $C_{max}$ (ng/ml) | 15.9 ± 4.6 | 16.1 ± 5.0 |
| $t_{max}$ (h) | 3.0 (1.67 – 9.0) | 4.0 (2.0 – 9.0) |
| $t_{½}$ (h) | 40 ± 8 | 43 ± 10 |

The ratio of $AUC_{0\text{-t}}/AUC_{inf}$ were all above 80%, except in two cases for the Reference treatment (2 x 79.6%).

The results of the statistical analysis are listed in table 2.

**Table 2**: Statistical evaluation on olanzapine pharmacokinetic variables

| | $AUC_{(0\text{-t})}$ | $AUC_{(0\text{-inf})}$ | $C_{max}$ |
|---|---|---|---|


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| | | | |
|---|---|---|---|
| Ratio's (test/ref) | 1.00 | 0.98 | 1.01 |
| 90% CI | 0.95 – 1.06 | 0.93 – 1.04 | 0.93 – 1.09 |
| CV% | 10.5% | 10.9% | 16.2% |

N.S.: not statistically significant;

**Study B0507 (10 mg orodispersible tablet):**

- Methods

STUDY DESIGN

This was a single-dose, 2-way cross-over study. Twenty-eight healthy non-smoker subjects, 21 males and 7 females, aged 18 - 50 years, were included in this study. Each subject received a single dose (1 x 10 mg orodispersible tablet) of both the test and reference olanzapine formulations after overnight fasting. The tablet was placed on the subject's tongue to be dissolved. After 30 seconds, and after a mouth check, the subject should drink 240 ml water. Fasting was continued for 4 hrs after dosing. For each subject there were 2 dosing periods, separated by a washout period of 21 days.
Blood samples were taken pre-dose and up to 168 hours post administration.

TEST AND REFERENCE PRODUCTS

Olanzapine 10 mg orodispersible tablets (Teva, Hungary) were compared to Zyprexa Velotab 10 mg tablets.

POPULATION(S) STUDIED

Twenty-eigth healthy subjects, twenty-one males and seven females, aged 18 - 50 years, all non-smokers, were included in this study. One subject (no.10) was withdrawn prior to Period II because of adverse events (i.e. pain at right shoulder and drowsiness), and one subject (no. 22) withdrew prior to Period II for personal reasons. Twenty-six subjects completed the study entirely, and were included in the analysis.

ANALYTICAL METHODS

Plasma samples were analysed for olanzapine using LC-MS/MS. The method was validated and a validation report was provided.

PHARMACOKINETIC VARIABLES

Olanzapine $AUC_{(0\text{-inf.})}$ and $AUC_{(0\text{-t})}$ were calculated by linear trapezoidal method. $C_{max}$ and $t_{max}$, were derived directly from concentration-time-curve. Elimination rate constant was estimated from the slope of the regression line using the terminal data points of the semi-logarithmic plasma concentration - time curve. $T_{½}$ was calculated as $0.693/k_{el}$.

STATISTICAL METHODS

The 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated for natural logarithm-transformed $C_{max}$, $AUC_{(0\text{-t})}$, and $AUC_{(0\text{-inf})}$ by ANOVA . Treatment, period, sequence, and subjects within sequence were included by the applicant into the 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.
The $AUC_{0\text{-inf,}}$ $AUC_{0\text{-t}}$, and $C_{max}$ of test and reference were also tested by assessor for bioequivalence using a different system..The least square means and the 90% CI of the (test/reference) ratios were calculated by ANOVA GLM procedure with period, treatment (test or reference) and subject within sequence as independent variables. The values were logarithmically transformed before ANOVA analysis.

- Results

The pharmacokinetic variables of olanzapine of the test and reference product are shown in Table 3. All pre-dose samples were below LoQ.


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**Table 3**. Pharmacokinetic variables of olanzapine of the test and reference (as mean ± s.d.; $t_{max}$ as median (range)).

| n=26 | Olanzapine Teva 10 mg orodispersible tablet dose 10 mg Test | Zyprexa® Velotab 10 mg orodispersible tablet dose 10 mg Reference |
|---|---|---|
| $AUC_{(0-t)}$ (ng.h/ml) | 554 ± 158 | 530 ± 150 |
| $AUC_{(0-inf)}$ (ng.h/ml) | 592 ± 175 | 569 ± 170 |
| $C_{max}$ (ng/ml) | 13.9 ± 3.9 | 12.7 ± 2.9 |
| $t_{max}$ (h) | 4.0 (1.0 – 12.0) | 5.3 (2.0 – 12.0) |
| $t_{½}$ (h) | 41 ± 8 | 42 ± 8 |

The ratio of $AUC_{0-t}/AUC_{inf}$ were all above 80%.

The results of the statistical analysis are listed in table 4.

**Table 4**: Statistical evaluation on olanzapine pharmacokinetic variables

| | $AUC_{(0-t)}$ | $AUC_{(0-inf)}$ | $C_{max}$ |
|---|---|---|---|
| Ratio's (test/ref) | 1.05 | 1.04 | 1.09 |
| 90% CI | 1.01 – 1.09 | 1.00 – 1.08 | 1.04 – 1.15 |
| CV% | 7.1% | 7.1% | 10.0% |

N.S.: not statistically significant;

**Study A37552 (20 mg orodispersible tablet):**

- Methods

STUDY DESIGN

This was a single-dose, 3-way cross-over study. Thirty healthy male non-smoker subjects, aged 21 - 44 years, were included in this study, of which 27 completed the study. Each subject received a single dose (1 x 20 mg tablet) of both the test (orodispersible tablet) and reference olanzapine formulations (Reference: orodispersible tablet and film coated tablet). The orodispersible tablet were administered without water, while the film coated tablet was administered in solid form with 240 ml water. All formulations were administered after overnight fasting. Fasting was continued for 4 hrs after dosing. For each subject there were 3 dosing periods, separated by a washout period of 21 days. Blood samples were taken pre-dose and up to 144 hours post administration.

TEST AND REFERENCE PRODUCTS

Olanzapine 20 mg orodispersible tablets (Teva, Hungary) were compared to Zyprexa Velotab 20 mg orodispersible tablets, and to Zyprexa 20 mg film coated tablets.

POPULATION(S) STUDIED

Thirty healthy male subjects, aged 21 - 44 years, all non-smokers, were included in this study. Three subjects were excluded. Subject 7 was excluded, because of vomiting in Period I within 5 hours after administration of the tablet, subject 19 withdrew prior to Period II for personal reasons, and subject 26 was withdrawn during Period I because of adverse events (e.g. hypotension, dizziness and palor). Subject 24 withdrew prior to Period III for personal reasons, but data obtained in Period I and II were used in the statistical analysis. Thus, twenty-six subjects completed the study entirely, while twenty-seven subjects completed Period I and II.


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ANALYTICAL METHODS

Plasma samples were analysed for olanzapine using LC-MS/MS. The method was validated and a validation report was provided.

PHARMACOKINETIC VARIABLES

Olanzapine $AUC_{(0\text{-inf.})}$ and $AUC_{(0\text{-t})}$ were calculated by linear trapezoidal method. $C_{max}$ and $t_{max}$, were derived directly from concentration-time-curve. Elimination rate constant was estimated from the slope of the regression line using the terminal data points of the semi-logarithmic plasma concentration - time curve. $T_{½}$ was calculated as $0.693/k_{el}$.

STATISTICAL METHODS

The 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated for natural logarithm-transformed $C_{max}$, $AUC_{(0\text{-t})}$, and $AUC_{(0\text{-inf})}$ by ANOVA. Treatment, period, sequence, and subjects within sequence were included by the applicant into the 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.

The $AUC_{0\text{-inf,}}$ $AUC_{0\text{-t}}$, and $C_{max}$ of test and reference were also tested by assessor for bioequivalence using a different system. The least square means and the 90% CI of the (test/reference) ratios were calculated by ANOVA GLM procedure with period, treatment (test or reference) and subject within sequence as independent variables. The values were logarithmically transformed before ANOVA analysis.

- Results

The pharmacokinetic variables of olanzapine of the test and reference products are shown in Table 5. All pre-dose samples were zero in period 1 and 2, but in period 3, 1 subject had pre-dose olanzapine concentrations of less than 0.51 ng/ml, which was less than 3% of the maximal plasma concentration.

**Table 5**. Pharmacokinetic variables of olanzapine of the test and reference (as mean ± s.d.; $t_{max}$ as median (range)).

| n=27 | Olanzapine Teva 20 mg orodispersible tablet dose 20 mg Test | Zyprexa® 20 mg orodispersible tablet dose 20 mg Reference B | Zyprexa® 20 mg tablet dose 20 mg Reference C# |
|---|---|---|---|
| $AUC_{(0\text{-t})}$ (ng.h/ml) | 967 ± 221 | 879 ± 212 | 948 ± 198 |
| $AUC_{(0\text{-inf})}$ (ng.h/ml) | 1037 ± 246 | 955 ± 227* | 1009 ± 218 |
| $C_{max}$ (ng/ml) | 24.9 ± 5.8 | 24.2 ± 6.9 | 25.5 ± 6.1 |
| $t_{max}$ (h) | 6.0 (1.67 – 12.0) | 4.33 (1.67 – 12.0) | 6.0 (2.33 – 12.0) |
| $t_{½}$ (h) | 35 ± 5 | 34 ± 5 | 36 ± 5 |

*n=26, because the elimination phase was not log linear; # n=26

The ratio of $AUC_{0\text{-t}}/AUC_{inf}$ were all above 80%, except in 1 case for Reference B treatment.

The results of the statistical analysis are listed in tables 6 and 7.

**Table 6**: Statistical evaluation on olanzapine pharmacokinetic variables:
Test versus Reference B (Zyprexa orodispersible tablet).

| | $AUC_{(0\text{-t})}$ | $AUC_{(0\text{-inf})}$ | $C_{max}$ |
|---|---|---|---|
| | | | |


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| | | | |
|---|---|---|---|
| Ratio's (test/ref) | 1.11 | 1.10 | 1.05 |
| 90% CI | 1.04 – 1.17 | 1.04 – 1.16 | 0.96 – 1.14 |
| CV% | 12.7% | 12.3% | 19.1% |

N.S.: not statistically significant;

**Table 7**: Statistical evaluation on olanzapine pharmacokinetic variables:
Test versus Reference C (Zyprexa tablet).

| | $AUC_{(0-t)}$ | $AUC_{(0-inf)}$ | $C_{max}$ |
|---|---|---|---|
| Ratio's (test/ref) | 1.03 | 1.04 | 0.99 |
| 90% CI | 0.97 – 1.09 | 0.98 – 1.10 | 0.91 – 1.08 |
| F-test between | | | |
| treatments | p=0.014 | p=0.03 | N.S. |
| Subjects | P<0.001 | p<0.001 | p<0.001 |
| Periods | N.S. | N.S. | N.S. |
| CV% | 12.7% | 12.3% | 19.1% |

N.S.: not statistically significant;

- **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 products Zyprexa and Zyprexa Velotab. The design of the submitted bioequivalence studies is considered adequate and the data of these studies sufficiently demonstrate that the tested formulations intended for marketing are bioequivalent to the innovator products.

Based on the submitted bioequivalence studies the Olanzapine Teva 10 mg film coated tablet is considered bioequivalent with the Zyprexa 10 mg film-coated tablet, the Olanzapine Teva 10 mg orodispersible tablet is considered bioequivalent with the Zyprexa Velotab 10 mg orodispersible tablet, and the Olanzapine Teva 20 mg orodispersible tablet is considered bioequivalent with the Zyprexa Velotab 20 mg orodispersible tablet and the Zyprexa 20 mg tablet. The orodispersible tablets can be taken with or without water, because in both cases bioequivalence to the reference product has been proven by the applicant. The results obtained for the 10 mg film coated tablet and the 10 and 20 mg orodispersible tablets can be extrapolated to the other strengths.

**Post marketing experience**

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

## 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**


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A Risk Management Plan has not been 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 is not required.

- **PSUR**

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

- User consultation

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

## 6. Overall conclusions, benefit/risk assessment and recommendation

**Overall conclusion and Benefit/risk assessment**

The application contains adequate quality, 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**

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


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