SCIENTIFIC DISCUSSION

1. Introduction

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

Olanzapine, a thienobenzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. As atypical antipsychotics are generally classified those drugs, which in contrast to classical antipsychotics (e.g. haloperidol), have greater affinity for serotonin 5-HT_{2A} receptors then for dopamine D_2 receptors and cause fewer extrapyramidal symptoms (EPS) and improve negative symptoms.

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

2. Quality aspects

Introduction

Zalasta is presented in the form of tablets and orodispersible tablets.

The tablets contain 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg of olanzapine as active substance. Other ingredients are lactose monohydrate, powdered cellulose, pregelatinised starch, maize starch, colloidal anhydrous silica and magnesium stearate.
The orodispersible tablets contain 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg of olanzapine as active substance. Other ingredients are mannitol, microcrystalline cellulose, crospovidone, low-substituted hydroxypropylcellulose, aspartame, calcium silicate, and magnesium stearate.

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 yellow crystalline powder without odour, practically insoluble in water, freely soluble in chloroform, soluble in dichloromethane and very slightly soluble in methanol. Solubility in aqueous media decreases with increasing of pH. Polymorphism has been observed for olanzapine.

- Manufacture

The manufacturing of olanzapine consists of synthesis and crystallization. Olanzapine of the same quality can be synthesized by two synthesis routes, which are equivalent in term of the pharmaceutical quality of the active substance. Olanzapine in a stable and reproducible polymorphic form is obtained by crystallization process.

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

The active substance specification includes tests for appearance, solubility (Ph Eur), identification (UV, IR), clarity and degree of opalescence (Ph Eur), degree of coloration of liquids (Ph Eur), loss on drying (Ph Eur), sulphated ash (Ph Eur), heavy metals (Ph Eur), related substances (HPLC), content of olanzapine (potentiometer titration), residual solvents (GC-HS), particle size (laser diffraction).

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 evaluated and found to be acceptable from the point of view of safety.

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

- Stability

Stability is being studied on pilot batches packed in mini-size simulation of the intended market containers. The stability study conditions, numbers of batches tested and testing frequency are in accordance with the relevant ICH/CHMP guideline. The conditions are: 25 °C/60 % RH and 40 °C/75 % RH.
Seven batches of olanzapine were put on long-term and accelerated stability testing conditions. A photostability study was performed on one batch (of samples stored for 24 months at 25 °C/60 % RH according to ICH Guideline. To identify degradation products of the drug substance the applicant has performed stress testing.
The parameters investigated are appearance, clarity and degree of opalescence of liquids, degree of coloration of liquids, loss on drying, assay of olanzapine and related compounds.
The proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

Medicinal Product

Tablets

- Pharmaceutical Development

The purpose of development of this pharmaceutical form was to achieve a highly bioavailable and stable dosage form, bioequivalent with reference medicinal product coated tablet. The emphasis of development work was also to achieve good content uniformity of the drug substance, optimal physical properties of the tablets, simplicity and reproducibility of technological processes

During formulation development the following aspects were evaluated: water vapour sorption of olanzapine, compatibility of the drug with excipients, flowability, compactability, lubricity, appearance, disintegration time and dissolution rate.

The bioequivalence study was performed with 10 mg strength since the composition of all strengths is proportional. The product composition used in the bioequivalence study was the same as intended for marketing. The composition of Zalasta tablets is different to the reference product but there are no relevant differences that would result in different safety profile. Similarity between the tablets and the reference medicinal product Zyprexa coated tablets has been shown by comparison of dissolution and impurity profile.

Dissolution profile testing in media with different pH was performed in order to predict *in vivo* release of olanzapine from the tablets. When developing tablets of other strengths, the same dissolution

method was applied and comparable *in vitro* dissolution profiles of olanzapine were determined for all strengths. The development and selection of the dissolution test method is suitable.

Different mixtures of olanzapine and excipients and many tablet formulations prepared by direct compression were studied and stress tested.

The excipients used are celactose (lactose monohydrate, powdered cellulose), pregelatinised starch, maize starch, colloidal anhydrous silica and magnesium stearate. The excipients are conventional and meet the requirements in Ph. Eur. Lactose monohydrate is manufactured from bovine milk. The supplier confirms that the milk used in the manufacture of the lactose is sourced from healthy animals under the same conditions as for human consumption.

Tablets are packed in blister packs consisting of cold formed OPA/AL/PVC film and heat sealing aluminium foil. The suitability of packaging was demonstrated in the stability studies.

- Manufacture of the Product

The manufacturing process includes weighing, mixing, sieving and compressing.

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 appearance, content uniformity (UV-VIS), water (Ph Eur), hardness (Ph Eur), disintegration (Ph Eur), identification of the active substance (UV, TLC), related substances (HPLC), dissolution, (Ph Eur), content of olanzapine and microbial purity (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 of five batches of pilot and production size for all strengths submitted confirm satisfactory uniformity of the product at release.

- Stability of the Product

Three pilot batches of 5, 10, 2.5 and 20 mg tablets packed in intended market containers were placed on stability under ICH conditions. The stability testing of 2.5, 7.5, 15 and 20 mg tablets is performed according to the reduced testing (bracketing design) following ICH guideline Q1D. The batches were tested for appearance, disintegration, assay, dissolution and microbiological purity of the tablets except requirements for related substances and total related substances, water and hardness and microbiological purity. They have were exposed to 25º C/60% RH for 48 months for 5 and 10 mg tablets and for 24 months for 2.5 and 20 mg tablets and 40º C / 75% RH for 6 months for all strengths. A photostability study was performed on one batch of 5 mg tablets stored according to ICH Guideline (Q1B).
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 purpose of development work was to develop drug product which would be comparable and bioequivalent to Zyprexa Velotab orodispersible tablets and possesses the following properties: disintegration in mouth spontaneously in contact with saliva, pleasant taste and good mouth feel.
The selection of excipients was the most critical step to achieve fast disintegration of the tablet in the mouth and pleasant mouth feel. Different mixtures of olanzapine and excipients and many tablet formulations were studied and stress tested.

The product composition used in the bioequivalence study was the same as intended for marketing. The composition of Zalasta orodispersible tablets is different to the reference product but there are no relevant differences that would result in a different safety profile. A bioequivalence study was performed on the 20 mg strength because the composition of all strengths is proportional.

Dissolution profile testing was performed in media with different pH in order to predict *in vivo* release of olanzapine from the orodispersible tablets. When developing orodispersible tablets of other strengths, the same dissolution method was applied and comparable *in vitro* dissolution profiles of olanzapine were determined for all strengths. The development and selection of the dissolution test method is suitable.

The excipients used are mannitol, microcrystalline cellulose, crospovidone, low-substituted hydroxypropylcellulose, aspartame, calcium silicate, and magnesium stearate. Most excipients comply with the Ph. Eur. Low-substituded hydroxypropylcellulose LH-21 and calcium silicate comply with USP/NF since they do not have monograph in Ph. Eur.

The orodispersible tablets are packed in blister packs consisting of cold formed OPA/AL/PVC film and heat sealing aluminium foil. The suitability of packaging was demonstrated in the stability studies.

- Manufacture of the Product

The manufacturing process is a standard wet granulation and includes weighing, granulation, drying, sieving, mixing and compressing.

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 appearance, content uniformity (HPLC), water (Ph Eur), hardness (Ph Eur), disintegration (Ph Eur), identification of the active substance (HPLC, TLC), related substances (HPLC), dissolution, (HPLC), content of olanzapine (HPLC), and microbial (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 five batches of pilot and production size for all strengths except 7.5 mg (four batches) submitted confirm satisfactory uniformity of the product at release.

- Stability of the Product

Three pilot batches of 5, 10, 2.5 and 20 mg tablets and two pilot batches of 7.5 mg packed in the intended market containers and in bulk on stability under ICH conditions. The stability testing of 5, 7.5, 10, 15 and 20 mg orodispersible tablets is performed according to the reduced testing (bracketing

design) following ICH guideline Q1D. The batches were tested for appearance, disintegration, assay, dissolution, related substances, total related substances, water, hardness, and microbiological purity. They have were exposed to 25º C/60% RH for 12 months for 5 and 20 mg and for 6 months for 7.5 mg and 40º C / 75% RH for 6 months 5 and 20 mg and 7.5 mg.

A photostability study was performed on one batch of 5 mg and 20 mg tablets in blisters stored for 12 months at 25 °C/60 % RH according to the ICH Guideline (Q1B), light source: Option 2, condition during test 25 °C/40 % RH (available 8 days results).

Based on the 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 both drug products 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 both the tablets and orodispersible tablets should have a satisfactory and uniform performance in the clinic.

3. Non-Clinical aspects

Zalasta tablets and Zalasta orodispersible tablets are generic medicinal products, having the same qualitative and quantitative composition in active substance (olanzapine) and the same pharmaceutical forms as their respective reference medicinal products Zyprexa and Zyprexa Velotab. Pharmacodynamic, pharmacokinetic and toxicological properties of olanzapine are well characterized. 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.

This application is being made under Article 10.1 (generic) of Directive 2001/83/EC for Zalasta 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg tablets and Zalasta 5 mg, 10 mg, 15 mg, and 20 mg orodispersible tablets , and Article 10.3 (hybrid) for Zalasta 7.5 mg orodispersible tablets, whereas the additional strength 7.5 mg is not authorized in Zyprexa Velotab.

4. Clinical Aspects

Introduction

The rapporteur 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 6 different strengths for the tablet form and 5 different strengths for the orodispersible tablet form. The Applicant has in fact provided only one bioequivalence study with one strength for each of the two formulations. To support the exemption, appropriate statements, justification and biopharmaceutic studies reports using *in vitro*-dissolution techniques with standard media for the two pharmaceutical forms and strengths in question, in comparison with the respective form of the reference product - Eli Lilly Deutschland GmbH Zyprexa tablets and Zyprexa Velotab orally disintegrating tablets - have been presented and are satisfactory (see Section Additional Data).

Clinical studies
To support the application, the Applicant has submitted two bioequivalence studies, one for each of the two pharmaceutical forms in question. These studies are described in the Pharmacokinetics section below.

Pharmacokinetics
As the application deals with two dosage forms, tablets and orodispersible tablets, and the application dossier contains two independent reports, the assessment of particular bioequivalence aspects is presented in two separate sections that follow.

Pharmacokinetic study – tablets

- Methods

For the tablets, a single-dose bioequivalence study was performed in fasting healthy volunteers in comparison with the originator product, indirectly covering the submitted range of strengths under the bibliographic dose linearity claims described in the "Exemption" and "Additional data" sections. The objective of the bioequivalence study was to compare the relative single-dose bioavailability of Krka and Eli Lilly (Zyprexa) 10 mg olanzapine tablets under fasting conditions.

STUDY DESIGN
For the tablets, a comparative, open-label, randomized, single-dose, 2-way crossover bioavailability study of Krka 10 mg olanzapine tablets compared to Eli Lilly 10 mg olanzapine tablets (Zyprexa) was performed in 22 healthy adult male volunteers plus additional 2 alternates under fasting conditions. The study was designated as Olanzapine Protocol 012645. The study was conducted using the services of a Contract research Organization. The study began on 22nd January 2002 and ended on 12th February 2002. The protocol and informed consent forms were reviewed and approved by an Institutional Review Board (IRB) committee convening and all subjects signed an informed consent form prior to dosing in the first period.

All 24 subjects completed the clinical phase of the study. In each period, the subjects were housed from the evening before dosing until after the 48-hour blood draw and were to return for the 72-, 96-, 120- and 144-hour blood draws. A single oral 10 mg dose was administered in each period of the study with 240 mL water. Single oral 10 mg doses were separated by a washout period of 14 days. Blood samples were collected up to 144 hours post administration.

TEST AND REFERENCE PRODUCTS
The Bioequivalence study (report no: 012645 #27669) was performed with Olanzapine 10 mg tablets (Krka) and the reference product Zyprexa (Eli Lilly) 10 mg tablets.

Test Product A: Olanzapine 10 mg tablets; Manufactured by KRKA d.d.

Reference B: Zyprexa (olanzapine) 10 mg film tablets; Manufactured by Eli Lilly.

The study and the archiving of essential documents were performed in accordance with stipulations of the Protocol, Declaration of Helsinki, and all confidential statements and especially to the Note for Guidance on GCP (CPMP/ICH/135/95). The accepted EEC standards of GLP were followed.

POPULATION(S) STUDIED

The study was performed in 22 healthy male volunteers and 2 alternates.

ANALYTICAL METHODS

Bioanalytical, Mass Spectrometry has determined the concentrations of olanzapine in human plasma using high performance liquid chromatography with mass spectrometric detection.

The Bioanalytical portion of this study was conducted between February 14, 2002 and February 25, 2002. The dossier includes analytical report providing results and supporting documentation of study sample analyses, in addition to standard curves and quality control sample data.

The analytical method for the determination of olanzapine in human plasma was developed based on LC/MS/MS detection and was properly validated.

PHARMACOKINETIC VARIABLES

The AUC0-t, AUCinf, AUC/AUCinf, Cmax, tmax, half-life and kel pharmacokinetic parameters were calculated for plasma olanzapine as follows:

AUC 0-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.

AUCinf: The area under the plasma concentration versus time curve from time 0 to infinity.

AUCinf was calculated as the sum of the AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.

AUC/AUCinf: The ratio of AUC 0-t to AUCinf.

Cmax: Maximum measured plasma concentration over the time span specified.

tmax: Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.

kel: Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero plasma concentrations).

t1/2: The apparent first-order terminal elimination half-life was calculated as 0.693/kel.

STATISTICAL METHODS

Statistical and pharmacokinetic analyses were performed on data from 22 subjects. Descriptive statistics were calculated using the usual measures of central tendency and dispersion. The analysis of variance (ANOVA) model included sequence, period and formulation as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals for the difference between drug formulation least-squares means (LSM) were derived from the analyses of the ln-transformed parameters AUC 0-t, AUCinf and Cmax.

- Results

The pharmacokinetic results for olanzapine in plasma are listed below.

Table 1. Pharmacokinetic parameters

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	475,85	512,27	12.296	5,913	37,64
Reference	470,52	510,01	11,772	6,595	38,72
***Ratio (90% CI)**	101.0% (97.4 - 104.8%)	100.3% (96.9 - 103.9%)	104.4% (98.2 - 110.9%)	N/A	N/A
CV (%)	7,3%	7,0%	11,7%		

$AUC_{0-\infty}$ 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***

Ratios of LSM (90% Confidence Intervals)

Parameter	Olanzapine 10 mg tablets (KRKA) (A) vs. Zyprexa (Eli Lilly) (B)
AUC 0-t	101.0% (97.4 - 104.8%)
AUCinf	100.3% (96.9 - 103.9%)
Cmax	104.4% (98.2 - 110.9%)

The results derived from the analyses of the ln-transformed AUC 0-t, AUCinf and Cmax pharmacokinetic parameters for olanzapine in plasma, adjusted for non-zero pre-dose concentrations in Period 2 are presented in the dossier. The adjusted concentration, pharmacokinetic parameter and ratio analysis tables are also presented to form the basis of the claim than the non-zero concentrations which were all below 2% of the Cmax do not influence the integrity of data in the study.

The ratios of least-squares means (with 90% confidence intervals) for the parameters AUC 0-t, AUCinf and Cmax for adjusted data were 101.1% (97.4 -105.0%), 100.4% (96.9 - 104.2%) and 104.5% (98.3 - 111.0%), respectively. The mean tmax values for the KRKA and Eli Lilly products were 5.913 and 6.595 hours, respectively. As expected, these results were similar to those obtained with unadjusted data, since the observed non-zero pre-dose concentrations were less than 2% of their respective Cmax in all cases. Hence, the conclusion of this study was not affected by the non-zero pre-dose concentrations observed.

Safety Assessment: No serious adverse events occurred during the conduct of this study.

- Pharmacokinetic Conclusion for Tablets

The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax for olanzapine in plasma were within the 80-125% acceptance range.

The bioequivalence study Olanzapine Protocol 012645 was well designed, conducted and reported. The validity of the data was confirmed by the positive results of the GCP inspection focusing on the laboratory phase of the study.

Based on the presented bioequivalence study Olanzapine 10 mg tablets, Manufactured by Krka d.d. (Novo Mesto, Slovenia) is considered bioequivalent with ZyprexaTM (olanzapine) 10 mg film tablets, Manufactured by Eli Lilly. The results of this study with the 10 mg formulation can be extrapolated to the other strengths 2.5, 5, 7.5, 15 and 20 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Following the CHMP request, the Applicant provided an acceptable and exhaustive explanation of the participants selection and the impact of the selection procedure on the overall results.

Pharmacokinetic Study – Orodispersible tablets

- Methods

For the orodispersible tablets, a single-dose bioequivalence study was performed in fasting healthy volunteers in comparison with the originator product, indirectly covering the submitted range of strengths under the bibliographic dose linearity claims described in the "Exemption" and "Additional data" sections. The objective of the bioequivalence study was to compare the relative single-dose bioavailability of Krka and Eli Lilly (Zyprexa Velotab) 20 mg olanzapine orodispersible tablets under fasting conditions.

Study design

For the orodispersible tablets, a comparative, open-label, randomized, single-dose, 2-way crossover bioavailability study of Krka 20 mg olanzapine orally disintegrating tablets compared to Eli Lilly Zyprexa Velotab 20 mg was performed in 24 healthy adult males and additional 2 alternates under fasting conditions.
The study, designated Protocol AA25817, was conducted using the services of a Contract Research Organization. The study was conducted in Canada, and the duration was as follows: Period 1 dosing: 26-Mar-2005; Period 2 dosing: 16-Apr-2005, Last clinical procedure conducted on a subject: 22-Apr-2005, and Report Date: 05-Jul-2005.
All subjects were in a fasted state following a 10-hour overnight fast. There was a 21-day washout interval between the 2 dose administrations. Period 1 was run on Eastern Standard Time and Period 2 was run on Daylight Saving Time. The subjects were confined to the clinic through the 48-hour post dose events and returned for the 72-, 96-, 120- and 144-hour events during each study period.

Test and reference products

Investigational Product(s):

Product A (tested product): Olanzapine 20 mg orodispersible tablets, Manufacturer: Krka, d.d., Novo mesto;

Product B (reference product): Zyprexa VeloTabTM 20 mg orodispersible tablets (olanzapine); Manufacturer: Lilly Deutschland GmbH (Eli Lilly);

Population(s) studied

The bioequivalence study was an open-label, randomized, single-dose, 2-way crossover comparative bioavailability study performed on 24 healthy adult non-smoking male subjects and 2 alternates. A total of 26 male subjects were dosed and all 26 subjects completed the clinical phase of the study.

The subjects were screened within 28 days prior to study enrolment. The screening procedure included medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build, and history of tobacco use. Each subject received a physical examination, vital signs measurements (heart rate, blood pressure, temperature, and respiratory rate), a 12-lead electrocardiogram (ECG), and laboratory tests which included haematologic, hepatic, and renal function (haematology, serum chemistry, urinalysis, HIV antibody screen, Hepatitis B surface antigen screen, Hepatitis C antibody screen, and a urine drug screen for opiates, amphetamines, barbiturates, benzodiazepines, cocaine, and cannabinoids).

On the evening prior to each dosing, each subject was screened for cocaine, cannabinoids, and alcohol.

All 26 subjects completed the clinical phase of the study. In each period, the subjects were housed from at least 10 hours before dosing until after the 48-hour blood draw and returned for the 72-, 96-, 120- and 144-hour blood draws during each study period. Single oral 20 mg olanzapine doses were separated by a washout period of 21 days. Protocol deviations were noted and no impact on the integrity was claimed.

Analytical methods

The concentrations of olanzapine in human plasma (EDTA) were determined using high performance liquid chromatography with mass spectrometric detection. Study samples were received as part of protocol number AA25817. Sample analysis was conducted between 29-Apr-2005 and 19-May-2005. The Analytical Report included in the dossier provides the results and supporting documentation from the analysis of study samples as well as standard curve and quality control sample data.

In a GLP compliance statements, the Contract Research Organization (CRO) analytical facility confirmed that this study was performed in compliance with the Standard Operating Procedures (SOP) in place in the bioanalytical laboratory and provided the pertinent SOPs in the dossier.

To ensure the integrity of the reported data, the bioanalytical laboratory verified all results. The Quality Assurance unit of the same laboratory audited the study. A Quality Assurance statement was then issued and is included in the dossier.

This report reflects the raw data and has been reviewed for completeness and accuracy.

Pharmacokinetic Variables

As per protocol, PK and statistical analyses were performed on data from 24 subjects that completed the study.

The AUC 0-t, AUCinf, AUC/AUCinf, Cmax, tmax, half-life and kel pharmacokinetic (PK) parameters were calculated for plasma olanzapine as follows:

AUC 0-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.

AUCinf: The area under the plasma concentration versus time curve from time 0 to infinity.

AUCinf was calculated as the sum of the AUC 0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.

AUC/AUCinf: The ratio of AUC 0-t to AUCinf.

Cmax: Maximum measured plasma concentration over the time span specified.

tmax: Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.

kel: Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g. three or more non-zero plasma concentrations).

t1/2: The apparent first-order terminal elimination half-life was calculated as 0.693/kel.

STATISTICAL METHODS

Descriptive statistics were calculated using the usual measures of central tendency and dispersion. Analyses of variance (ANOVA) were performed on the In-transformed PK parameters AUC 0-t, AUCinf and Cmax. The ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals for the ratios of least-square means (LSM) were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed PK parameters AUC 0-t, AUCinf and Cmax.

- Results

The PK results for olanzapine in plasma are listed below.

Table 1. Pharmacokinetic parameters

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	1080,4	1148,0	28,41	4,792	35,44
Reference	1099,5	1171,1	27,71	4,833	36,32
***Ratio (90% CI)**	98.6% (96.1 - 101.1%)	98.4% (95.8 - 101.0%)	102.9% (97.3 -108.9%)	N/A	N/A
CV (%)	5,2%	5,3%	11,4%	N/A	N/A

$AUC_{0-\infty}$ 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*

Ratios of LSM (90% Confidence Intervals

Parameter	KRKA (A) vs. Lilly Deutschland GmbH (Zyprexa VelotabTM) (B)
AUC 0-t	98.6% (96.1 -101.1%)
AUCinf	98.4% (95.8 - 101.0%)
Cmax	102.9% (97.3 -108.9%)

Safety Considerations: No serious adverse events occurred during the conduct of this study.

- Pharmacokinetic Conclusion for Orodispersible Tablets

The 90% confidence intervals derived from the analyses of the ln-transformed PK parameters AUC 0-t, AUCinf and Cmax for olanzapine in plasma were within the 80-125% acceptance range.

The bioequivalence study Protocol AA25817 was well designed, conducted and reported. The validity of the data was confirmed by the positive results of the GCP inspection focusing on the laboratory phase of the study.

Based on these results olanzapine 20 mg orodispersible tablets, manufactured by Krka d.d. (Novo Mesto, Slovenia) is considered bioequivalent with Zyprexa Velotab 20 mg orodispersible tablets, manufactured by Lilly Deutschland GmbH (Eli Lilly). The results of this study with the 20 mg formulation can be extrapolated to the other strengths 5, 7.5, 10 and 15 mg, according to the conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Following the CHMP request, the Applicant provided acceptable and exhaustive explanation of the participants selection and the impact of these procedures on the overall results.

Pharmacodynamics
Not applicable.

Additional data
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.

Intrinsic dissolution was performed in 0.1 M Hydrochloric acid, in 0.01 M Hydrochloric acid and in purified water.

In vitro **dissolution studies- tablets and orodispersible tablets**

Dissolution rates of olanzapine from OLANZAPINE tablets, ZYPREXA tablets, OLANZAPINE orodispersible tablets and ZYPREXA VeloTab 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 6.8.
The concentrations of olanzapine were measured by an UV spectrophotometric method for the tablets and by validated HPLC method for the orodispersible tablets.

Comparable *in vitro* dissolution profiles of olanzapine were determined between OLANZAPINE tablets 10 mg and ZYPREXA tablets 10 mg and between OLANZAPINE orodispersible tablets 20 mg and ZYPREXA VeloTab tablets 20 mg in all investigated media.

The monograph states that olanzapine orodispersible tablets can be administered with or without water. Since these two routes of administration could lead to different oral/sublingual absorption, during evaluation the CHMP objected that the administration of the orodispersible tablets without water had to be thoroughly investigated. The applicant presented acceptable and exhaustive justification that the product's administration without water has only minimal effect on the oral absorption.

- Conclusions on clinical studies

The number and types of the BE studies are appropriate considering the nature of the pharmaceutical forms investigated and the pharmacokinetic properties of olanzapine. The application deals with two fast-release dosage oral forms, containing olanzapine as a psychotropic substance with a relatively long half life (> 30 hrs). In such cases, single dose bioequivalence studies in fasting healthy volunteers are appropriate and are compliant to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98. The comparative bioavailability studies presented are

potent indicators of the performance of Zalasta in relation to the reference medicinal product in a clinical setting.

In-vitro dissolution studies are in the studied case justified for the development and strength exemption purposes and provide additional insight in the olanzapine release characteristic of the tablets and orodispersible tablets. Sufficient comparative information in relation to the release characteristics of the originator product was provided in the dossier. According to the results of the bioequivalence studies, the in-vitro dissolution studies results are consistent with the in-vivo results and support the overall conclusions on the bioequivalence of the tested Zalasta formulations with respect to the reference medicinal product.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country. The company must ensure that the system is in place and functioning before the product is placed on the market.

5. Pharmacovigilance

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

- **Risk Management Plan**

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 Zalasta tablets and Zalasta orodispersible tablets should follow PSURs submission schedule for the reference medicinal product.

Discussion on Clinical aspects

Tablets
Based on the presented bioequivalence study Zalasta 10 mg tablets manufactured by Krka d.d. is considered bioequivalent with Zyprexa 10 mg film tablets manufactured by Eli Lilly. Bioequivalence study Olanzapine Protocol 012645 was well designed, conducted and reported. The validity of the results of this study was confirmed by the positive results of the GCP inspection focusing on the laboratory phase of the study.

Orodispersible tablets
Based on the presented bioequivalence study (Protocol AA25817) Zalasta 20 mg orodispersible tablets, manufactured by Krka, d.d. is considered bioequivalent with Zyprexa VeloTab 20 mg orodispersible tablets (olanzapine), manufactured by Lilly Deutschland GmbH (Eli Lilly). The bioequivalence study was well designed, conducted and reported. The validity of the results of this study was confirmed by the positive results of the GCP inspection focusing on the laboratory phase of the study.

General conclusion - *in vitro* dissolution data
According to the results of the bioequivalence studies, the in-vitro dissolution studies results are consistent with the in-vivo results and support the overall conclusions on the bioequivalence of the tested Zalasta formulations with respect to the reference medicinal products.

- 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 patiens /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

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Zalasta in the treatment of schizophrenia is positive. 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 was favourable and therefore recommended the granting of the marketing authorisation.