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COMPARATIVE, SINGLE-DOSE, 2-WAY CROSS-OVER BIOAVAILABILITY STUDY OF TWO OLANZAPINE 10 MG TABLET FORMULATIONS IN HEALTHY VOLUNTEERS UNDER FASTING CONDITIONS

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ABSTRACT

Objectives: Olanzapine is an atypical antipsychotic that is approved across Europe, the USA, and in many other countries for oral treatment of schizophrenia and acute manic episodes in patients with bipolar disorder as well as for maintenance therapy to prevent recurrence in responders. The objective of the present study was to compare the pharmacokinetics of two 10 mg tablet formulations of Olanzapine following a single oral dose in healthy volunteers under fasting conditions, as per the European Medicine Agency (EMA) guidelines to grant marketing authorization.

Methods: This study was a randomized, open-label, two-treatment, two-period, two-sequences, single-dose, cross-over design with a washout period of 14 days. Both the test and the reference products were administered as 10 mg tablets with 240 mL of water after an overnight fast in each study period. A total of twenty blood samples were collected before dosing and within 144 hours after drug administration. Adverse events were monitored, recorded, and evaluated by investigators throughout the study.

Results: Of the 24 healthy adult male subjects enrolled, all of them completed both study periods. The geometric mean ratio 90% confidence intervals (CI) for fasting Cmax, AUC0-t, and AUC0-infinity were 94.83-113.71%, 95.04-105.69% and 95.94-107.00%, respectively. The 90% CI for the ratios of the three primary pharmacokinetic parameters (using log-transformed data) were within the range of 80-125%, meeting the regulatory criteria for bioequivalence.

Conclusions: The generic Olanzapine was bioequivalent to the reference formulation. It was well tolerated and provides an acceptable alternative to the reference drug.

Keywords: Olanzapine, bioequivalence, healthy subjects

INTRODUCTION

Olanzapine (CAS 132539-06-1) is an antipsychotic, antimanic, and mood stabilizing agent that demonstrates a broad pharmacologic profile across a number of receptor systems. In preclinical studies, Olanzapine exhibited a range of receptor affinities for serotonin 5 HT2A/2C, 5 HT3, 5 HT6; dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M1-M5; α1 adrenergic; and histamine H1 receptors. This medication has been approved for the treatment of schizophrenia

and is effective in maintaining clinical improvement during continuation therapy in patients who have shown an initial treatment response. Additionally, Olanzapine is indicated for the treatment of moderate to severe manic episodes. In patients whose manic episodes have responded to Olanzapine treatment, Olanzapine is used for the prevention of recurrence in patients with bipolar disorder. [1, 2] Olanzapine is generally well tolerated, and although it is associated with a higher incidence of weight gain, it has the advantage of a low incidence of extrapyramidal symptoms and causes a minimal perturbation of prolactin levels in comparison to the conventional antipsychotics. [3–5]

The pharmacokinetics of Olanzapine is linear and dose-proportional within the approved dosage range. Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Olanzapine is highly bound to plasma proteins (>90%), predominantly to albumin and α1-acid-glycoprotein. Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activity than Olanzapine in animal studies. The predominant pharmacologic activity is from the parent drug. Its mean plasma half-life in healthy individuals is 33 hours (ranges from 21 to 54 hours). After administering radiolabeled Olanzapine, approximately 60% of the radioactivity is excreted in urine and 30% in the feces. The mean apparent plasma clearance is 26 L/h (ranges from 12 to 47 L/h). The plasma clearance of Olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on Olanzapine clearance and half-life is insignificant in comparison to the overall variability between individuals. [6, 7]

The objective of this study was to compare the bioavailability of two 10 mg tablet formulations of Olanzapine in healthy adult male subjects, as required by regulatory authorities for marketing of a generic product.

MATERIALS AND METHODS

2.1 Subjects

Subjects were recruited from the volunteer's database of the Department of Preclinical and Clinical Pharmacology & Toxicology, Faculty of Medicine, Skopje, Republic of North Macedonia. They signed informed consent prior to participation in the study and underwent screening evaluations to determine eligibility within 14 days prior to dosing in the first study period. Subjects were included if they were male, aged 18-55 years (both inclusive), had body mass index within the range of 18-28 kg/m^2, normal physical examination and vital signs, clinically acceptable findings on hematology and biochemistry tests, serology, urinalysis, 12-lead electrocardiogram (ECG), agreed not to use any vitamins or herbal products for 2 weeks, as well as any prescription and over-the-counter medications for 4 weeks prior and during the course of the study, had no history of alcohol and/or drug abuse within the past 1 year, were non-smokers and able to communicate and cooperate with the investigators and the study personnel.

Subjects with known sensitivity or idiosyncratic reaction to Olanzapine or benzodiazepines or other antipsychotic drugs, or subjects with history of severe hypersensitivity reactions (like angioedema) to any drugs, as well as history or presence of glaucoma or any clinically significant illness, particularly gastrointestinal, liver or kidney disease, or any other conditions that may affect drug bioavailability were excluded from the study. Additionally, subjects who had participated in another clinical study, had donated or lost more than 450 mL of blood within 2 months, or donated plasma or platelets within 2 weeks before the study, or were found positive for human immunodeficiency virus, hepatitis B, hepatitis C were excluded from the study. Based on urine alcohol tests before and/or drug abuse tests, performed at check-in for each study period, and those who were unable or unwilling to comply with the provisions of the protocol were excluded from the study.

Moreover, subjects were also not included if they refused to abstain from consuming food for at least 10 hours prior to study medication administration until 5 hours post-dose, as well as drinking any fluid for at least 1 hour prior to

study medication administration until at least 1 hour post-dose in each study period (except 240 mL of water given during study medication administration).

All subjects were confined within the facility for at least 12 hours prior to dosing until 24 hours post-dose in each study period. They returned to the study center at 48, 72, 96, 120, and 144 hours post-dose for ambulatory blood sample collection in both study periods.

2.2 Study design

Bioequivalence assessment was performed at the Department of Preclinical and Clinical Pharmacology & Toxicology, Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia. The trial was designed as a randomized, open-label, balanced, two-treatment, two-period, two sequence, single-dose, crossover study under fasting conditions with a 14 day washout period between two study periods. The protocol was approved by the Ethical Committee at the Faculty of Medicine, Skopje and the study, carried out outside of the European Union, met the ethical requirements of Directive 2001/20/EC. This study was conducted as per the principles of the Declaration of Helsinki and adhered to the Good Clinical Practices guidelines, EMA regulations, and relevant national legislation. [8–11]

All subjects received information from a qualified investigator about the study. Written informed consent was obtained from each subject before the initial screening assessment. Eligible subjects were given a subject number to maintain the confidentiality of their identity. The volunteer's records and other source data was archived according to the archiving regulations and facilities of the study center.

2.3 Treatment and randomization

Eligible subjects received a single oral dose of 1 x 10 mg tablet of Olanzapine, either test (T: Olanzapine from Replekfarm AD (Batch Number: PB0108)) or reference (R: Zyprexa® from Eli Lilly Nederland B.V. (Batch Number: A550347)) formulation, according to the randomization schedule in each study period, with 240 mL of water under fasting conditions. A mouth and hands check was done immediately after drug administration to assess the compliance to the procedure. The order of receiving the test or reference drug for each subject during both periods was determined according to the randomization code (sequences TR or RT), ensuring an equal number of subject allocation to sequence, which maintained random allocation of drugs over the period and sequence. The study was conducted on healthy subjects in order to reduce variability not related to differences between products.

2.4 Blood sampling

Twenty blood samples were withdrawn at following time points in each study period: 0 (pre-dose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, 96, 120 and 144 hours post-drug administration. Blood samples were collected into heparinized polypropylene tubes and centrifuged within 10 minutes. The plasma samples were stored frozen at −18 ± 4ºC until assayed. The total volume of blood withdrawn over the duration of the study for each subject did not exceed 300 mL.

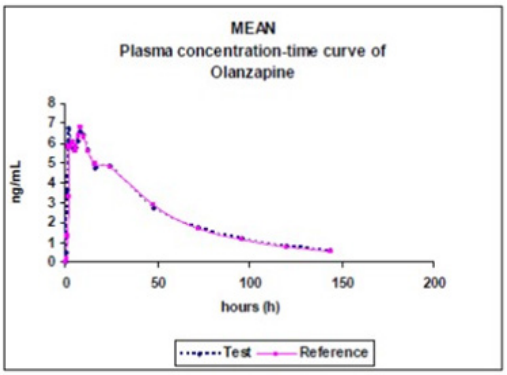
2.5 Bioanalytical methods

Determination of Olanzapine in plasma was performed by a validated HPLC-MS/MS analytical method. Linearity was tested at nine calibration standard points and ranged from 0.032 ng/mL (lower limit of quantification) up to 32.960 ng/mL (upper limit of quantification). Within- and between-run accuracy ranged from 0.03 % to 14.97 %. The extraction recovery of Olanzapine was constant for the three tested quality control concentration levels averaging 85 %, 91%, and 89% respectively. The extraction recovery of the internal standard was also constant, averaging 90% - 94%. Results of the stability experiments were always within ±15% of deviation, and thus it was proven that no degradation of Olanzapine and/or the internal standard occurred under the different storage conditions.

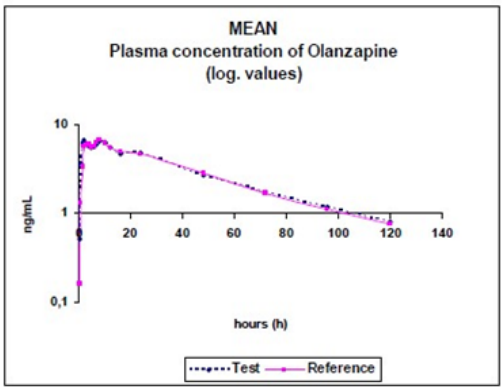
2.6 Pharmacokinetic and statistical analysis

Pharmacokinetic analysis was conducted according to a non-compartmental method using the drug concentration profiles and the actual sampling time points with the KINETICA™ 4.4 software (Innaphase Corporation, USA). The maximum plasma concentration (C_{max}) and the time of reaching the maximum plasma concentration (T_{max}) were directly derived from the plasma concentration-time curves of Olanzap-

ine (Figure 1). Area under the plasma concentration-time curve from time zero until the last sampling time point (AUC_{0-t}) and the area under the curve of the plasma concentrations extrapolated to infinity (AUC_{0-inf}) were calculated according to the linear trapezoidal rule up to last sampling point Clast and extrapolated to infinity, respectively. The extrapolation was performed by adding Clast/β, β denoting the last-squares estimate at the terminal elimination constant and Clast denoting the concentration value at tlast estimated by terminal logarithmic linear regression. The elimination rate constant (Kel) and the elimination half-life ($t_{1/2}$) were also calculated as additional pharmacokinetic variables.



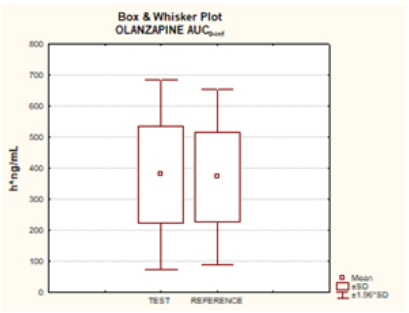
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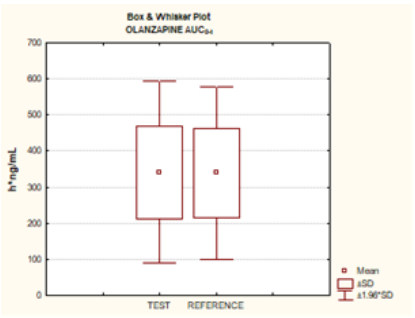
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Figure 1. *Mean Olanzapine plasma concentration versus time curves of the test and reference formulations (a- mean values; b- log transformed data)*

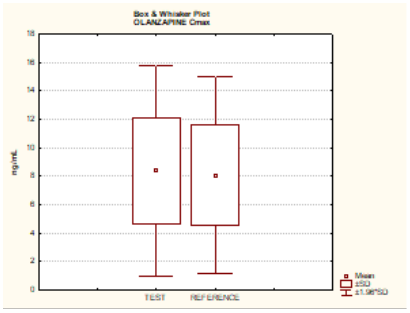
The pharmacokinetic parameters underwent a descriptive statistical evaluation. The ratio between the calculated values with the corresponding 25-75% distribution levels for each pharmacokinetic parameter of the test and reference drug was represented by Box-Whisker plots (Figure 2). Statistical comparisons between the pharmacokinetic variables for AUC_{0-inf}, AUC_{0-t} and C_{max} were completed via analysis of variance (ANOVA) using the model for a two-period, two-treatment crossover design by the computer program EquivTest 2.0 (Statistical Solutions). The model takes into account sources of variation due to subjects, treatments, sequence and periods.



a



b



c

Figure 2. *Comparison of the primary pharmacokinetic parameters: AUC0-inf (a), AUC0-t (b) and Cmax (c) between the test and the reference formulations (Box & Whisker Plots).*

The information obtained from ANOVA served to calculate the correspondent 90% confidence intervals for the primary pharmacokinetic parameters: AUC_{0-inf}, AUC_{0-t} and C_{max} of the tested preparation as a ratio to the correspondent values of the reference preparation using parametric and nonparametric methods with log-transformation of data. The same confidence intervals were additionally calculated by

the parametric Schuirmann's approach. [12] As a discrete variable, Tmax was analyzed by means of a nonparametric Wilcoxon-Matched Pairs test. The bioequivalence between the two Olanzapine products was concluded if the 90% confidence interval fell within the acceptable range of 80-125% for all three primary pharmacokinetic parameters: C_{max}, AUC_{0-t} and AUC_{0-inf}.

Considering the data in the literature that the intra-subject coefficient of variation for Cmax of Olanzapine is approximately 15%, a sample size of 22 subjects was expected to demonstrate bioequivalence with a power of 80% using the 90% confidence intervals (80-125% criteria). Expecting certain dropouts and/or withdrawals, a sample size of 24 subjects was considered to be appropriate to meet the bioequivalence criteria. [12–14]

RESULTS

3.1 Demographic characteristics

A total of 24 subjects were enrolled in this study. All of them completed both study periods and were included in the pharmacokinetic and statistical analyses. The demographic characteristics of the study population are presented in Table 1.

3.2. Pharmacokinetic evaluation

All twenty-four dosed subjects completed both study periods and were included in the pharmacokinetic evaluation. Figure 1 provides graphic representations of mean plasma concentration-time profiles and mean logarithmic plasma concentration-time profiles of the test and reference formulations of Olanzapine. The pharmacokinetic parameters of the volunteers are summarized for both test and reference formulations in Table 2. The arithmetic mean (SD) of C_{max} for the reference and test formulations was 8.05 (3.53) and 8.38 (3.76) ng/mL, respectively. For the reference and test formulations, the AUC_{0-t} was found to be 339.51 (122.65) and 341.60 (128.88) ng×h/mL, while the AUC_{0-inf} was 371.97 (144.67) and 379.11 (155.03) ng×h/mL, respectively. The ratio between the calculated values with the corresponding 25-75% distribution levels for the primary pharmacokinetic parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) of the test and reference drug is represented by Box-Whisker plots (Figure 2).

3.3 Statistical evaluation

The results of the statistical analysis are presented in Table 3. No significant sequence, period, and treatment effects were observed for the primary pharmacokinetic parameters. The 90% CI of the ratios for the log-transformed values of C_{max}, AUC_{0-t} and AUC_{0-inf} were 0.9483-1.1371, 0.9504-1.0569 and 0.9594-1.0700, respectively. The results indicate that the test formulation was bioequivalent to the reference formulation with respect to all three primary pharmacokinetic parameters that were within the predefined bioequivalence range of 80.00-125.00% as per EMA guidelines.

3.4 Safety evaluation

Both formulations appear to be well tolerated by the study subjects after single oral dose of Olanzapine under fasting conditions. All registered adverse events (AEs) were recorded in the study source data and were evaluated by investigators. A total of 40 post-dose adverse events were reported by 23 (95.8%) of the 24 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group was as follows: 22 AEs reported by 66.7 % (n=16) of the 24 subjects who received the test formulation and 18 AEs reported by 62.5 % (n=15) of the 24 subjects who received the reference formulation. The safety profile was similar for the test and the reference formulation.

The most commonly reported AE was somnolence (35), followed by dry mouth (3), headache (1) and dysgeusia (1), all were attributed to the pharmacological action of Olanzapine. The relationship with the study medication was assessed as possible (21 cases) or probable (19 cases). The severity of the 28 AEs was graded as "moderate", whereas the other 12 AEs were graded as "mild". All AEs experienced during this study were resolved completely by the end of the study. No severe adverse events, serious adverse events, or deaths occurred during the study. Upon conclusion of the clinical portion of the study, the results from the subjects who completed end of study procedures, including laboratory tests and vital signs measurements confirmed the absence of significant changes in

Table 1. *Baseline characteristics of the volunteers*

N=24	Age (year)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean	38.1	179.58	85.37	26.45
SD	7.59	8.31	10.78	1.82

BMI = body mass index; SD = standard deviation; N = number of subjects

Table 2. *Pharmacokinetic parameters of Olanzapine estimated for the test and reference formulations.*

Pharmacokinetic parameters	Test formulation (N = 24)		Reference formulation (N = 24)	
	Mean	SD	Mean	SD
AUC_{0-inf} (ng×h/mL)	379.11	155.03	371.97	144.67
AUC_{0-t} (ng×h/mL)	341.60	128.88	339.51	122.65
C_{max} (ng/mL)	8.38	3.76	8.05	3.53
t_{max} (h)	5.27	3.78	6.17	2.97
Kel (1/h)	0.018	0.004	0.019	0.004
t ½ (h)	40.95	9.77	38.57	7.88

SD = standard deviation; N= number of subjects

Table 3. *90% Confidence intervals for the test and reference formulations.*

Pharmacokinetic parameters	90% Confidence interval		Within bioequivalence limits
	Lower limit	Upper limit	
AUC_{0-inf}	0.9594	1.0700	YES
AUC_{0-t}	0.9504	1.0569	YES
C_{max}	0.9483	1.1371	YES

the subjects' states of health. No new safety concerns related to administered formulations were raised during the conduct of this study.

DISCUSSION

Switching to generic antipsychotic may lead to a significant reduction in out-of-pocket cost and may be an attractive alternative, given that chronic therapy is required for the patients with schizophrenia and bipolar disorder. Additionally, recent research suggests that Olanzapine might be a promising treatment option for patients with anorexia nervosa and chemotherapy-induced nausea. [15-19] In view of this, a generic formulation of Olanzapine 10-mg tablets was developed and a bioequivalence was demonstrated with the reference formulation Zyprexa. To meet the regulatory requirements of bioequivalence, the study was conducted on healthy subjects in accordance with EMA guidance. Consistent with posology and administration, as given in the summary of product characteristics, bioequivalence was examined following the administration of Olanzapine in the fasting conditions as the rate and extent of Olanzapine absorption is not affected by food. [7, 8]

This study examined the bioequivalence of two 10 mg tablet formulations of Olanzapine in healthy adult male volunteers. The presented

results indicate that the generic and the reference formulations have similar pharmacokinetic profiles. Both formulations provided similar mean C_{max} values. Although it took slightly longer to reach the mean maximum concentration with the reference formulation (6.17 h) compared with the test product (5.27 h), this is not considered to be clinically relevant. More importantly, the measured AUC_{0-t} and AUC_{0-inf} values are not significantly different and have 90% confidence intervals within the standard acceptance bioequivalence range (80-125%). These data imply that similar Olanzapine exposure is achieved when individuals are switched between these two investigated products. The obtained results are comparable to those published in other pharmacokinetic studies with different generic Olanzapine formulations (powder for oral suspension, tablet, film-coated tablet, or dispersible tablet) and with a similar safety profile. [20–24]

The current study has some limitations. The sample size was relatively small, and it assessed bioequivalence in relatively young (38.1±7.6 years) and only male subjects, which certainly does not equate to the whole patient population. It is more difficult to identify possible differences between two formulations in patients with significant variability (other comorbidities, concomitant therapy, etc.) than in strictly controlled studies in healthy individuals. Therefore, further studies are needed to confirm these results in a patient population.

CONCLUSION

The test formulation (Olanzapine 10 mg tablets) manufactured by Replekfarm AD met the European regulatory criteria of bioequivalence as compared with the reference formulation Zyprexa® (Eli Lilly Nederland B.V.) after a single-dose administration in healthy volunteers under fasting conditions and was well tolerated. The switch to the test formulation seems to be safe and effective, and it may reduce the economic burden of treating psychiatric patients.

Abbreviations

AE- adverse event; AUC_{0-inf}- area under the curve of the plasma concentrations extrapolated to infinity; AUC_{0-t}- area under the plasma concentration-time curve from time zero until the last sampling time point; BMI- Body Mass Index; CI- Confidence Interval; C_{max}- maximum plasma concentration; EMA- European Medicines Agency; Kel- elimination rate constant; N= number of subjects; SD = standard deviation; SmPC- Summary of Product Characteristics; t ½- elimination half-life; T_{max}- time of reaching the maximum plasma concentration

Conflict of interest

The study investigators had no financial interests in the product or the manufacturer, but did receive research funding to perform the study.

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Резиме

КОМПАРАТИВНА, ДВОЈНО ВКРСТЕНА СТУДИЈА НА БИОРАСПОЛОЖИВОСТ НА ДВЕ ФОРМУЛАЦИИ ОЛАНЗАПИН ОД 10 MG ВО ОБЛИК НА ТАБЛЕТИ ПО ЕДНОКРАТНА АПЛИКАЦИЈА КАЈ ЗДРАВИ ДОБРОВОЛЦИ НА ГЛАДНО

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Цели: Оланзапинот е атипичен антипсихотик, кој е одобрен за употреба во Европа, во САД и низ светот за перорален третман на шизофренија и акутни манични епизоди кај пациенти со биполарни нарушувања, како и за терапија на одржување за превенција на повторно појавување на симптомите. Целта на оваа студија беше да се споредат фармакокинетските параметри на две формулации оланзапин од 10 mg во облик на таблети по еднократна апликација кај здрави испитаници на гладно, во согласност со водичите на Европската медицинска агенција (EMA) за добивање одобрение за промет на лек.

Методи: Студијата беше дизајнирана како рандомизирана, отворена, со два третмани, две секвенции, двојно вкрстена студија со еднократна апликација на лек и период од 14 дена помеѓу двата периода. Во секој период од студијата, тестираниот и референтниот производ беа аплицирани како таблети од 10 mg со 240 mL вода по период на гладување во текот на ноќта. Беа земени вкупно 20 примероци на крв во интервалот од пред дозирањето, па сè до 144 часа по администрацијата на лекот. Несаканите настани беа мониторирани, документирани и евалуирани од страна на истражувачите во текот на студијата.

Резултати: Сите 24 здрави машки доброволци што беа вклучени во студијата ги завршија двата периода од студијата. Односот на геометриските средни вредности за 90 % интервал на доверливост (CI) за фармакокинетските параметри одредени по апликација на лекот на гладно: Cmax, AUC0-t, и AUC0-infinity изнесуваа 94,83–113,71 %, 95,04–105,69 % и 95,94–107 %, соодветно. 90 % CI на односите на трите главни фармакокинетски параметри (со употреба на лог-трансформирани податоци) беа во опсег од 80 до 125 %, што одговара на регулаторните критериуми за биоеквивалентност.

Заклучок: Генеричкиот препарат на оланзапинот беше биоеквивалентен со референтната формулација, со добар безбедносен профил, поради што може да се смета за прифатлива алтернатива на референтниот лек.

Клучни зборови: оланзапин, биоеквиваленција, здрави доброволци