

Bioequivalence Study of Olanzapine 5 mg Orally Disintegrating Tablet Formulations in Healthy Thai Volunteers under Fasting Conditions

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Abstract

A comparative randomized, single dose, two-way crossover, open label study was carried out to assess bioequivalence and tolerability of test (ZOLAN GPO®) and reference (Zyprexa Zydis®) products of olanzapine 5 mg orally disintegrating tablets for interchangeability in the same quality and safety. Twenty-six male and female healthy Thai volunteers were enrolled in and completed the study. Blood samples were collected at predefined time points over 72 hours after oral administration under fasting conditions. Plasma concentrations of olanzapine were determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS), capable to quantify olanzapine in the range of 0.098-40.896 ng/mL. The pharmacokinetic parameters were calculated for test and reference products using non-compartmental analysis. Bioequivalence between the products was determined by calculating 90% CIs for the geometric mean ratio of C_{max} and AUC truncated at 72 hours (AUC_{0-72}) between the test and reference products using log-transformed data. Pharmacokinetics of olanzapine were in agreement with the literature data. No significant difference was found based on ANOVA; 90% confidence interval (92.67–106.38% for C_{max} and 95.36–103.81% for AUC_{0-72}) of test/reference ratio for tested parameters were found within bioequivalence acceptance range of 80.00-125.00%. Both treatments were well tolerated, and none of subjects developed any serious adverse events. It can be concluded that the ZOLAN GPO® is bioequivalent to Zyprexa Zydis® and can be used interchangeably.

Keywords: Olanzapine; Orally Disintegrating Tablet; Bioequivalence; Pharmacokinetics; LC-MS/MS

Introduction

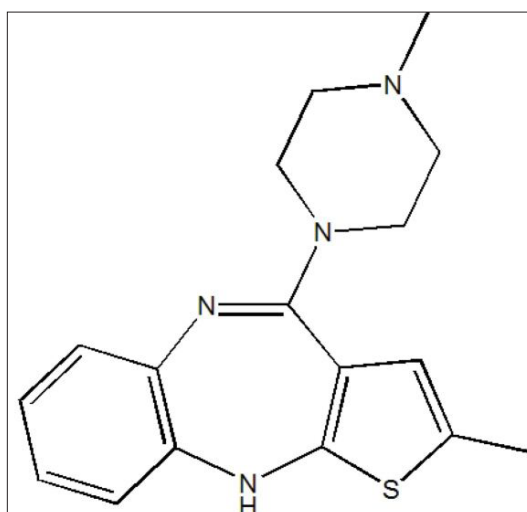


Figure 1: Chemical structure of olanzapine

Olanzapine is a thienobenzodiazepine derivative (Figure 1) exhibiting high-affinity antagonist for serotonin 5-HT_{2A/2C}, dopamine D₂, muscarinic M₁-M₃, histamine H₁ and α -1 adrenergic receptors. Olanzapine's antagonism of these receptors may explain the mechanism of action and adverse effects observed with this drug [1-3]. Olanzapine is an atypical antipsychotic

agent indicated for the treatment of schizophrenia in the acute phase and for the maintenance of treatment response [2]. Monotherapy of olanzapine or in combination with other therapeutic agents is recommended for the treatment of bipolar I disorder [1,3-5]. Olanzapine has demonstrated greater efficacy and safety over conventional drugs in several clinical trials. Most common adverse events are somnolence, constipation, weight gain, dizziness, asthenia, postural hypotension, personality disorder, akathisia, increased appetite, fatigue, abdominal pain, dyspepsia, and dry mouth [2,5,6]. However, fewer discontinuations due to such adverse events have been reported for olanzapine-treated patients [2].

Olanzapine is well absorbed with an oral bioavailability about 60%. Maximum plasma concentration (C_{max}) is attained within approximately 6 hours after oral administration and increased proportionally with the dose. Food does not significantly affect the rate and extent of absorption [1-8]. The drug exhibits high tissue distribution with a volume of distribution about 10-22 L/kg after a single oral dose. It is highly bound to human plasma proteins; albumin and α_1 -acid glycoprotein with bound fraction approximately 93% [2,3,5-8]. Direct glucuronidation and cytochrome P450 (mainly CYP1A2) mediated oxidation are the primary metabolic pathways. The major metabolite is 10-N-glucuronide [1-3,5,6,8]. Approximately 57% of olanzapine and its metabolites are recovered in the urine and partly (30%) in the feces. Elimination half-life is about 30 hours (ranges from 21-54 hours). The apparent plasma clearance value is about 25 L/hour (ranges from 12-47 L/hour) [2,3,5,7,8]. There are no pharmacokinetic differences between males and females, thus dose modification is not required [2]. However, the pharmacokinetics of olanzapine can be altered in elderly, smokers and patients with moderate hepatic insufficiency [9].

The Government Pharmaceutical Organization (GPO), Thailand had developed a generic product of olanzapine 5 mg orally disintegrating tablets at a reduced cost without affecting quality and safety to serve as an alternative choice for physicians and patients in Thailand. This bioequivalence study was conducted to provide supportive information on the bioequivalence and interchangeability between generic and innovator formulations, as well as to evaluate the safety of the formulations in healthy Thai volunteers.

Materials and Methods

Study products

ZOLAN GPO[®], olanzapine 5 mg orally disintegrating tablets (Lot No. S590123) manufactured by GPO, Thailand were used as the test product and Zyprexa Zydis[®], 5 mg orally disintegrating tablets (Lot No. 1594215A) manufactured by Catalent UK Swindon Zydis Ltd., United Kingdom were used as the reference product.

Subjects

The number of subjects was calculated by considering the assumptions of the maximum intra-subject variability for primary pharmacokinetic parameter of olanzapine about 19.1%, T/R ratio 95%, significant level 5%, power $\geq$ 90% and bioequivalence limits of 80.00-125.00% [10]. The calculation suggested that twenty-two subjects were sufficient for the study. Additional eight subjects were added to compensate for possible dropouts and withdrawals (rate of 30%). Thirty eligible volunteers were healthy Thai males and females at the age between 18 and 55 years with a body mass index between 18 and 25 kg/m². They were well informed and provided written informed consent before study participation at Pharmacy Service Center, Faculty of Pharmacy, Chiang Mai University, Thailand. All subjects were estimated to be healthy by assessment of medical history, physical and laboratory examinations such as complete blood count, hematocrit, hemoglobin, fasting blood sugar, blood urea nitrogen, serum creatinine, alkaline phosphatase, ALT, AST, total bilirubin, total protein, albumin, HBs antigen, Anti-HCV, Anti-HIV, urine analysis, chest X-ray and ECG. Female subjects were not pregnant with negative pregnancy test, or breastfeeding at all time of the study, and were required to use an acceptable method of contraception (non-hormonal method) throughout the study.

Exclusion criteria included any history of hypersensitivity to olanzapine or any of the excipients; a history or presence of any disease; clinically significant illness in 4 weeks before study initiation; a history of suicide attempt and/or present positive result of screening questionnaire for depression and suicidal risk from National Center for Suicide Prevention of Thailand; physician-diagnosed orthostatic hypotension; participation in any other clinical trials within the past 3 months; a recent history of harmful use of alcohol or drug abuse; consumption of any medication, vitamins or dietary supplements within past 2 weeks before the study; smoking within 6 months prior to dosing; consumption of any grapefruit, pomelo or orange-based products within 48 hours prior to dosing; or consumption of xanthine containing products within 48 hours prior to dosing.

Study design

The study was designed as a randomized, single dose, two-treatment, two-period crossover trial. After an overnight fasting for at least 10 hours, a single dose of either test or reference product was orally administered to each subject in each period as per the randomization schedule. Before administration, subjects were instructed to wet their mouth by swallowing 20 mL of water. The entire tablet was placed on their tongue immediately after water administration. Then the tablet was left on their tongue for 2 minutes to allow complete tablet dispersion in saliva. Subjects were asked to swallow the drug-dispersed saliva. Food and water intake was not allowed after 4 hours and 1 hour post-dose, respectively. Further meals, snacks and beverage were provided at

appropriate time during housing period. Subjects were not allowed to rise without assistance and were instructed to be in supine or semi-recumbent position during first 10 hours post-dose. After a washout period of 21 days, the study was repeated in the same manner to complete the crossover design. Adverse events were monitored throughout the study based on direct questioning, clinical examinations (eg. vital signs, chest X-ray, and ECG), suicidal assessment, and laboratory examinations.

The clinical study protocol was reviewed and approved by the Research Ethics Committee 2, Faculty of Medicine, Chiang Mai University, Thailand on 23 November 2017 (letter no. 437/2560). The study was conducted as per the protocol, ICH 'Guidance on Good Clinical Practice', Declaration of Helsinki and Standard Operation Procedures (SOPs) of Clinical Trial Unit of Sriphat Medical Center, Faculty of Medicine, Chiang Mai University, Thailand.

Blood sampling

In each period, a total of 24 blood samples were collected at pre-dose (0 hour), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose. At each time point, approximately 5 mL of blood was drawn through an indwelling intravenous cannula in the forearm vein or fresh vein puncture using syringe. The drawn sample was transferred into dipotassium ethylenediaminetetraacetate (K_2EDTA)-containing vacutainer and subsequently centrifuged at relative centrifugal force (rcf) 3000 ± 100 for 5 minutes at 4 °C to separate plasma. From 5 mL of each blood sample, approximately 2 mL of plasma was achieved. The separated plasma was transferred into two different pre-labeled polypropylene tubes as first lot and second lot for respective sample analysis and incurred sample reanalysis. The plasma samples were stored upright at -55 °C or colder until analysis. The storage duration of frozen plasma samples was not more than 123 days based on validated data of long-term stability.

Sample analysis and incurred sample reanalysis

The plasma samples were analyzed at bioanalytical facility of GPO, Thailand. Samples of each subject from two study periods were analyzed altogether. The study personnel involved in sample bioanalysis were blinded from randomization schedule during analytical phase. Plasma concentration of olanzapine in the study samples were determined by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method which is validated as per the Guideline on bioanalytical method validation of European Medicines Agency (EMA) [11] and the U.S.FDA Guidance for Industry Bioanalytical Method Validation [12]. Olanzapine and Olanzapine-d8, an internal standard were extracted from the plasma using liquid-liquid extraction technique modified from Elshafeey *et al.*, [13].

Briefly, 50 μ L of each olanzapine-d8 (10 ng/mL) and 0.1M sodium hydroxide was added to 250 μ L of plasma sample. Thereafter, 3 mL of extraction mixture (tert-butyl methyl ether: hexane (80:20)) was added and vortexed for 3 minutes. The sample was centrifuged at rcf 3500 for 5 minutes at 10 °C. The plasma layer was flash-frozen and the organic layer was transferred to another tube and subsequently evaporated at 50 °C to dryness. The residue was reconstituted with 250 μ L of mobile phase and 5 μ L of sample was injected into the LC-MS/MS system. The LC component (Nexera™, Shimadzu Corporation, Japan) consisted of CBM-20A lite system controller, LC-30AD binary pump, DGU-205A degasser, SIL-30AC autosampler and CTO-20AC column oven. The chromatographic separation was performed using an ACE 3 C18 analytical column maintained at 50 °C. An isocratic mobile phase consisted of 5mM ammonium acetate buffer (pH 6.5) and acetonitrile (10:90) and was eluted at a flow rate of 1 mL/minute. The detection was done using MS/MS detector (TSQ Quantum Ultra equipped with electrospray ion source, Thermo Fisher Scientific Inc., USA) in the multiple reaction monitoring (MRM) transition of m/z 313.15 to 256.06 and m/z 321.20 to 261.10 for olanzapine and olanzapine-d8, respectively. Data analysis was performed using Xcalibur™ 3.0.63.3 and LCQuan™ 2.9.0.34 (Thermo Fisher Scientific Inc., USA).

Incurred sample reanalysis (ISR) was performed to ensure the reliability and reproducibility of the study data. The selection procedure and number of incurred samples were following the EMA guideline on bioanalytical method validation [11]. Study samples having concentrations close to C_{max} and in the elimination phase of each subject in each period were chosen and reanalyzed. The concentration values from incurred sample reanalysis were not used in pharmacokinetic calculation. Bioanalysis was carried out according to the Principles of Good Laboratory Practice and SOPs of Research and Development Institute, GPO, Thailand.

Pharmacokinetic and statistical analysis

Olanzapine plasma concentrations were analyzed as a function of time. The pharmacokinetic parameters were computed for each formulation using non-compartmental model of Phoenix WinNonlin software version 6.4 (Pharsight Corporation, USA). Area under the plasma concentration-time curve truncated at 72 hours (AUC_{0-72}) and C_{max} were considered as the primary parameters and the time to maximum plasma concentration (t_{max}) was considered as the secondary parameter. Descriptive statistics were computed and reported for primary and secondary pharmacokinetic parameters of test and reference products. All concentration values below the lower limit of quantification were set as zero for the pharmacokinetic and statistical calculations. Study subjects who did not provide evaluable data for both of the test and reference products were excluded from analysis. The log-transformed AUC_{0-72} and C_{max} were subject to analysis of variance (ANOVA) for olanzapine. ANOVA model included sequence, formulation and period as fixed effects, and subject as a random effect. Sequence effect was tested using subject as error term. An F-test was performed to evaluate the statistical significance of the effects involved in the model at a significance level of 5% ($\alpha=0.05$). Values of

$t_{\max}$ were compared using nonparametric Wilcoxon signed-rank test ($p = 0.05$). Bioequivalence of the test and reference products was concluded, if the statistical results of 90% confidence interval (CI) for the ratio of the geometric least square mean (test/reference) for log-transformed AUC_{0-72} and $C_{\max}$ fell within the acceptance range of 80.00-125.00%. The statistical analysis was conducted using PROC GLM of SAS® version 9.4 (SAS Institute Inc., USA).

Results

Demographic characteristics of subjects

Thirty healthy adult Thai volunteers were enrolled and randomly divided into two groups; reference-test (RT) and test-reference (TR) groups which consisted of fifteen subjects per group. There were 8 females and 7 males in RT while 7 females and 8 males were in TR. The mean $\pm$ SD of age, weight, height, and BMI were 25.4 ± 3.6 years, 59.4 ± 8.1 kg, 1.65 ± 0.08 m, and 21.9 ± 2.1 kg/m². After dosing in period I, one subject was withdrawn from the study due to adverse event and safety concern. Two subjects were withdrawn before period II as they experienced one of the conditions in the exclusion criteria and additional one subject was withdrawn due to adverse event occurring during washout period. Therefore, twenty-six subjects completed the study and their plasma concentration data were used for pharmacokinetic and statistical analysis.

Sample analysis and incurred sample reanalysis

A total of 1326 plasma samples collected from 30 subjects were successfully analyzed. The precision and accuracy demonstrated by quality control samples in each analytical run ranged from 3.8 to 5.3% and 102.5 to 107.6%, respectively. A total of 122 plasma samples were chosen for incurred sample reanalysis. Out of 122 reanalyzed samples, 120 samples (98.4%) had percent difference between original and ISR concentrations less than 20% indicating good reproducibility of the method (Supplementary Material).

Pharmacokinetic and statistical analysis

Mean plasma concentration-time profiles after oral administration of test and reference products are illustrated in semi-logarithmic scale (Figure 2). The mean $\pm$ SD (N=26) values of studied pharmacokinetic parameters for test and reference products are summarized in Table 1. According to the results, olanzapine was well absorbed with the average peak concentrations at 11.2 ng/mL, which were attained in around 3 hours after administered for both test and reference products.

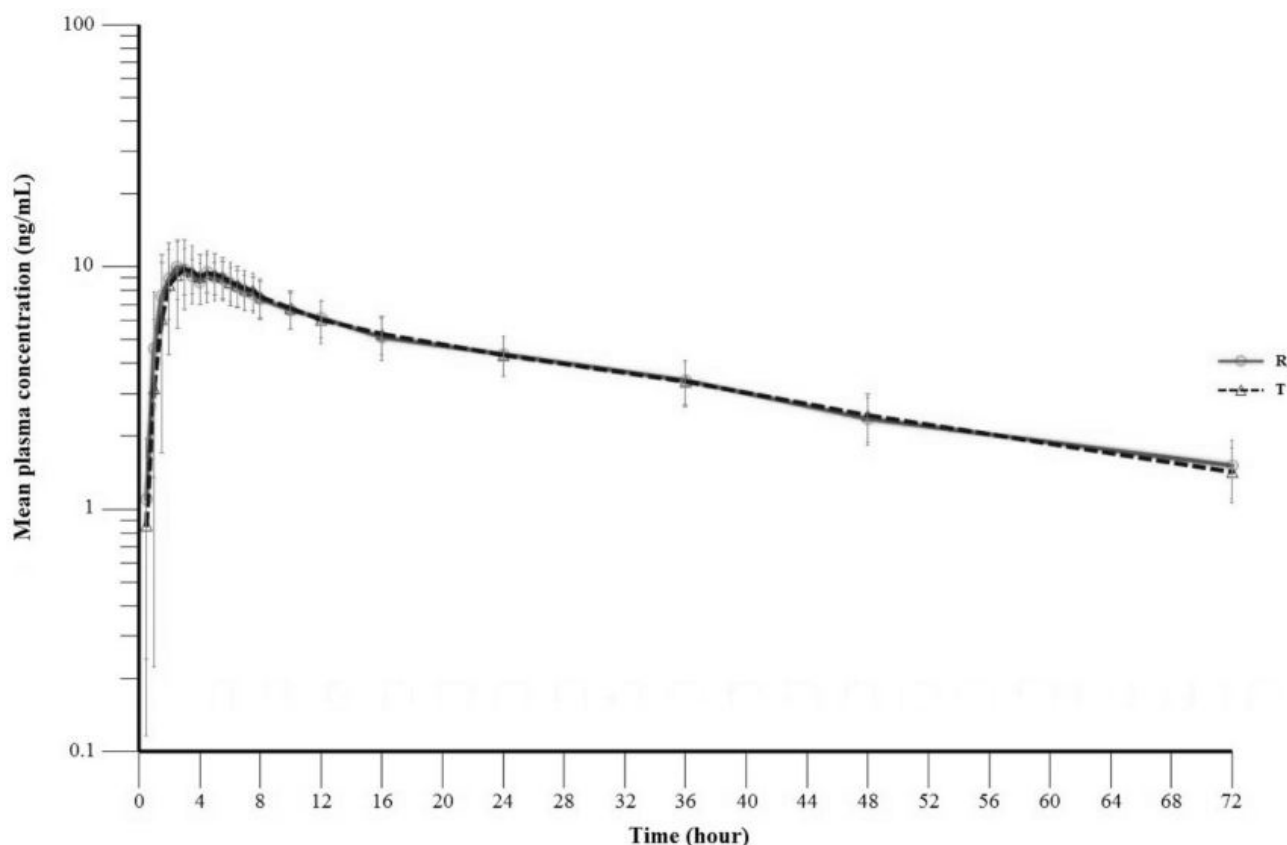


Figure 2: Plasma concentration-time profile (semi-logarithmic scale) after oral administration of the test (T) and reference product (R) in healthy Thai volunteers under fasting condition. Data is mean $\pm$ SD (N=26)

Parameters (Units)	Un-transformed data(mean±SD)	
	Test product	Reference product
AUC ₀₋₇₂ (hour.ng/mL)	277±51.2	277±47.0
C _{max} (ng/mL)	11.2±2.70	11.2±2.14
t _{max} (hour)*	3.25 (1.50,6.00)	2.75 (1.50,5.50)

*showed as median (min,max)

Table 1: Pharmacokinetic parameters of olanzapine in twenty-six healthy volunteers

Statistical analysis was performed on the data obtained from subjects who completed the study and provided evaluable data for both of the test and reference products (N=26). The ANOVA of sequence, period and treatment effect for log-transformed data of AUC₀₋₇₂ and C_{max} are presented in Table 2. The results indicated that these effects were statistically insignificant ($p > 0.05$). Two one-sided tests for bioequivalence were performed and 90% CIs for the geometric mean ratio of log-transformed AUC₀₋₇₂ and C_{max} between the test and reference formulations were calculated (Table 2). The 90% CIs of geometric mean ratio of AUC₀₋₇₂ (99.5 [95.36-103.81]) and C_{max} (99.3 [92.67-106.38]) were within the acceptance range of 80.00-125.00%. Wilcoxon signed-rank test demonstrated that there was a significant difference of median T_{max} between the test and reference products ($p = 0.03$).

Parameters	Ratio (90% CI)	Power	Intra subject CV (%)	ANOVA (p-value) variation source		
				Sequence	Formulation	Period
ln(AUC ₀₋₇₂)	99.5 (95.36-103.81)	100.0	8.9	0.7808	0.8393	0.7498
ln(C _{max})	99.3 (92.67-106.38)	100.0	14.6	0.9426	0.8612	0.6824

Table 2: Geometric mean ratio, 90% CI and ANOVA data of log-transformed pharmacokinetic parameter for test and reference products

Tolerability

Total of twenty-one adverse events were reported in thirteen subjects over two study periods. Eleven adverse events were reported in eight subjects who received the test product whereas ten adverse events were reported in eight subjects who received the reference product. All of adverse events are presented in Table 3. The first two frequently observed adverse events in this study were orthostatic hypotension and dizziness. All of the adverse events were assessed to be mild and moderate in intensity and 71% of adverse events were probably associated to the study drug. The details of the adverse events were reported to the Research Ethics Committee 2 of Faculty of Medicine, Chiang Mai University in a timely manner.

Adverse event	Reported adverse event incidence (N)	
	Test product	Reference product
Gastrointestinal disorders Nausea	0	1
Nervous system disorders Dizziness	3	1
Fainting and hypotension	1	0
Fainting and dizziness	0	1
Vascular disorders Orthostatic hypotension	3	5
Eye disorders Conjunctivitis	0	1
Respiratory, thoracic and mediastinal disorders Throat irritation and cough	1	0
Rhinorrhea	1	0
Rhinorrhea with low grade fever	1	0
Reproductive system disorders Dysmenorrhea	1	0
Skin and subcutaneous tissue disorders Herpes simplex labialis	0	1
Total adverse events	11	10
Total subjects developed adverse event	8	8

Table 3: List of adverse events

Discussion

Thirty subjects were enrolled in the study and four of them were not able to complete the study. According to subject number calculation, however, the data from twenty-six subjects were sufficient to demonstrate bioequivalence with adequate power. Based on the literature data on t_{max}, the sampling time point was designed to collect blood sample half-hourly up to first 8 hours

to capture the absorption phase of olanzapine, as well as to avoid $C_{\max}$ being the first point of a concentration time curve. The plasma concentration-time profiles of the test and reference products were comparable. Pharmacokinetics of olanzapine after administration of an orally disintegrating tablet was in agreement with the literature data [14]. In addition, the pharmacokinetic parameters obtained in this bioequivalence study were found to be similar to the published study in the same population [6]. However, the study in Indian volunteers showed significantly lower mean $C_{\max}$ values than that observed in this study whereas the $C_{\max}$ of olanzapine was achieved at greater $t_{\max}$ values (7.90 to 8.23 hours) compared with $t_{\max}$ observed in this study [8].

The $AUC_{0-\infty}$ was not calculated for olanzapine due to its long half-life. The AUC truncated at 72 hours was used for bioequivalence assessment for olanzapine because 72 hours should cover the absorption phase of immediate release dosage form. For long half-life drug, therefore, AUC_{0-72} could adequately describe and differentiate the biopharmaceutical performance between drug products [15]. Based on statistical inferences, there were no significant differences observed in AUC_{0-72} and $C_{\max}$ indicating bioequivalence between test and reference products. Even though the results of Wilcoxon signed-rank test showed the significant difference in median $t_{\max}$ between the test and reference products of olanzapine, neither rapid onset of action nor time-dependent adverse effect has been claimed for olanzapine. Therefore, the insignificant difference in median $t_{\max}$ may not necessarily require for the conclusion on bioequivalence of olanzapine formulations.

It has been established that olanzapine is a well-tolerated antipsychotic drug [2]. However, with concerning to the safety of study subjects, adverse events monitoring was performed closely throughout the study. The adverse events observed in this study have been commonly reported for the study drug. The incidence of adverse events reported after receiving test and reference products was similar. Only one subject was withdrawn by the physician due to drug-associated adverse event. According to safety evaluation, both treatments were well tolerated, and none of subjects developed any serious adverse events.

Conclusion

The test product (ZOLAN GPO®) and the reference product (Zyprexa-Zydis®) exhibited comparable pharmacokinetic profiles. In bioequivalence study in healthy Thai volunteers under fasting conditions, statistical comparison of AUC_{0-72} and $C_{\max}$ indicated that the two formulations of olanzapine were bioequivalent. Therefore, they can be used interchangeably and the same efficacy can be expected.

Acknowledgement

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