Pharmacokinetic and Bioequivalence Study of an Oral 8 mg Dose of Rosiglitazone Tablets in Thai Healthy Volunteers

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Background: *Rosiglitazone maleate is an antihyperglycemic agent in the thiazolidinedione class. It is indicated for the treatment of patients with type 2 diabetes mellitus. A new product of rosiglitazone has been developed. The pharmacokinetic in Thai subjects should be considered and the bioequivalent data of new generic product is required in order to assure the quality and performance.*

Objective: *To characterize the pharmacokinetics of rosiglitazone in Thai subjects and compare the bioequivalence of generic product of a single oral 8 mg rosiglitazone tablet with the innovator's product.*

Material and Method: *The present study was performed in 24 healthy Thai male volunteers. Each received a single oral dose of 8 mg rosiglitazone tablet. Double blind randomized two-way crossover design was used with two weeks washout period between treatments. After drug administration, a serial blood sample was collected over a period of 48 hours. Rosiglitazone plasma level was determined by HPLC with fluorescence detector. The pharmacokinetic parameters were determined by non compartment model. For bioequivalence determination, the difference of C_{max}, AUC_{0-t} and AUC_{0-inf} were analyzed by ANOVA and 90% confidence interval.*

Results: *The mean $\pm$ SD of pharmacokinetic parameters of generic product and the innovator's product were 0.82 $\pm$ 0.52 vs. 1.02 $\pm$ 1.50 hr of T_{max}, 796.51 $\pm$ 155.19 vs. 723.48 $\pm$ 134.69 ng/ml of C_{max}, 3.94 $\pm$ 0.80 vs. 3.87 $\pm$ 0.77 hr of $T_{½}$, 4,308.43 $\pm$ 1,006.28 vs. 4,135.66 $\pm$ 1,061.96 ng.hr/ml of AUC_{0-t}, 4,384.65 $\pm$ 1,035.15 vs. 4,183.87 $\pm$ 1,075.39 ng.hr/ml of AUC_{0-inf}, respectively. The 90% confidence interval of mean difference of C_{max}, AUC_{0-t} and AUC_{0-inf} (log transformed data) of generic product compared to the innovator's product were 98.42-122.18%, 97.28-109.66% and 97.79-110.30%, respectively. They were within the range of the acceptance criteria 80-125%.*

Conclusion: *Pharmacokinetic parameters of a single oral dose of 8 mg rosiglitazone tablet were characterized in Thai healthy subjects. These parameters showed that rosiglitazone was rapidly absorbed with a short elimination half-life. The two formulations of rosiglitazone were bioequivalent.*

Keywords: *Rosiglitazone, Pharmacokinetic, Bioequivalence*

J Med Assoc Thai 2010; 93 (6): 722-8
Full text. e-Journal: *http://www.mat.or.th/journal*

Rosiglitazone maleate is an oral antihyperglycaemic agent in the thiazolidinedione class. It binds with high affinity to peroxisome proliferator-activated receptor-γ (PPARγ); PPARγ isoforms are found in key target tissues for insulin action such as liver, adipose and skeletal muscle tissue. Activation of PPARγ is thought to result in the control of glucose production, transport and utilisation, and in the regulation of lipids. The results of PPARγ activation are reduction in hepatic glucose production and increased insulin dependent glucose uptake in fat and skeletal tissues. Rosiglitazone acts primarily by reducing insulin resistance, improves sensitivity to insulin in muscle and adipose tissues and decreases hepatic gluconeogenesis. It is indicated for the treatment of patients with type 2 diabetes mellitus with the affinity to PPARg receptor higher than pioglitazone and troglitazone[1-4,7].

After single oral dose, rosiglitazone was rapidly absorbed achieved peak concentration at 603 µg/l (ng/ml) within 0.75-1.0 hr and with AUC_{0-inf} of 2,930 µg.hr/l. Oral bioavailability is 99% (86-106%) and

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extensively protein bound (99.8%). Clearance after oral administration is rapid and the elimination half life is 3 to 4 hr. Excretion occurs mostly via the urine. Rosiglitazone is fully metabolized, mainly by CYP2C8 with N-demethylation, hydroxylation and further conjugation with sulfate and glucuronic acid. Fifteen metabolites of rosiglitazone were excreted mainly by urine (62%) and feces (23%). Renal impairment or aging did not result in clinically significant changes to the pharmacokinetics of rosiglitazone. Rosiglitazone did not interact with other drugs metabolized by CYP enzymes nor with drugs commonly used in patients with type 2 diabetes mellitus[1,4-6].

The recommended starting oral dose of rosiglitazone should be 4 mg once or twice daily as monotherapy and combination therapy with sulfonylurea or metformin, with or without food, together with diet and exercise regimens. The dosage may be increased as required to 8 mg/day as a single oral dose. Dosage adjustments are not required in elderly or in patients with renal impairment. It is generally well tolerated in patients with type 2 diabetes mellitus. However, patients with active liver disease or increased liver enzymes, ALT $\geq$ 2.5 times the upper limit of normal, should not receive rosiglitazone. Hepatic monitoring is required for all patients during therapy[1,7].

Currently, only the innovator's product (Avandia®, Glaxo) of a tablet containing rosiglitazone 8 mg is commercially available in Thailand. A new generic formulation of rosiglitazone 8 mg has currently been developed in Thailand. The comparison of bio-equivalent data of the new product with the innovator's product is required in order to assure its quality.

Material and Method

Test product

Test drug-products of rosiglitazone 8 mg tablets were used for in vivo bioequivalency study. One was the product of Unison Laboratories Co; Ltd. (Rosita®) lot no. T 08/5-423 and another was the innovator's product (Avandia®) lot no N 101 5A60.

Chemicals and reagents

Rosiglitazone and celecoxib (internal standard) were supplied by Unison Laboratories Co., Ltd. Acetonitrile HPLC grade and sodium acetate anhydrous were obtained from FLUKA, Switzerland.

Subjects

The present study was approved by the Ethical Committee of the Faculty of Medicine, Chulalongkorn University. Twenty four healthy Thai male volunteers aged between 18-45 years were included in the present study. All had normal body built with BMI between 18-25, weighting within $\pm$ 10% of ideal body weight. All subjects were in good health confirmed by physical and clinical laboratory examinations including serology, hematology and biochemical test. All subjects were abstained from other drugs intake and alcoholic consumption two weeks prior to and throughout the present study. Caffeine and caffeine containing beverage were not allowed 3 days prior to and throughout the present study. The methods and condition of the present study were clearly explained to all subjects. Informed consent was signed and obtained from each subject prior to entering the experiment. At least eight weeks before the first treatment, the subjects did not donate any blood or participate in any other clinical trial. The subjects with cigarette smoking, alcoholic intake and caffeine intake habit were excluded. Although the reports[2] showed hepatotoxicity of rosiglitazone was very low, liver function test was done in all subjects immediately after the present study.

Study design

The present study was carried out according to a randomized, two-treatment, two-period, two-sequence, single dose crossover design with two weeks of drug-free interval between the periods. Each subject was prepared in the fasted state approximately eight hours prior to the present study and randomly assigned to receive a single dose of 8 mg rosiglitazone with 200 ml of water. On the study day a standardized light lunch was consumed after the blood sampling at 4 hours. Blood samples were collected immediately before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24 and 48 hours after drug intake. The plasma were separated by centrifugation and stored at -70°C.

Sample preparation

Ten µl of celecoxib (internal standard) was added to 500 µl of plasma, mixing, and then 1.8 ml acetonitrile was added, and vortexed for 30 second. The samples were centrifuged at 4,000 rpm for 10 minutes at room temperature. The supernatant was transferred and evaporated to dryness with speed vacuum. Dried samples were reconstituted with 500 µl of mobile phase and the solution was centrifuged at 4,000 rpm for 10 minutes. Aliquot of 20 µl of supernatant was used for HPLC system.

Instrument and condition

Chromatography was carried out at room temperature on Shimadzu-HPLC system-10A series. Inersil ODS-3, a reverse phase column C18 (size 250 x 4.6 mm, i.d. 5 μm), was used. The mobile phase consisted of 50 mM acetate buffer (pH 4.5): acetonitrile (42: 58; v/v) flowing through the system at the rate of 1 ml/min. The HPLC column temperature was 40°C. Eluent was monitored by Fluorescence detector set at an excitation wavelength of 240 nm and emission wavelength of 380 nm and the sample injection volume was 20 μl.

Data analysis

Descriptive statistics (mean ± standard deviation (SD) and mean ± standard error (SEM) of the pharmacokinetic parameter were determined. C_{max} and T_{max} were taken directly from the individual concentration versus time data. The elimination rate constant (Kel) was estimated by log-linear least squared regression of the terminal part of the plasma concentration versus time curve. The area under the concentration versus time curve (AUC_{0-t}, AUC_{0-inf}) was calculated by the linear trapezoidal rule.

The comparison of bioavailability of the generic product of 8 mg rosiglitazone to the innovator's product was assessed using the relevant pharmacokinetic parameters, C_{max} and $AUC_{0-inf,}$ both were transformed to logarithmic scale for statistical analysis. The difference of the corresponding C_{max}, AUC_{0-t} and AUC_{0-inf} between two products were determined by Two Way Analysis of Variance (ANOVA) for a crossover design at the significant level of $\alpha = 0.05$. The 90% confidence interval (Two-one sided test) for the differences of C_{max}, AUC_{0-t} and AUC_{0-inf} means based on log transformed data were calculated.

The two products were considered to be bioequivalent when each 90% confidence interval was within 80-125%.

Adverse events

The subjects were requested to report all adverse events at baseline (predose), during and after drug intake, the subjects were questioned for adverse events by the medical staff. All adverse events encountered during the clinical study were reported on the Case Report Form. The severity of the adverse events were graded on a three-point scale (mild, moderate, severe) and report in detail as indicated on the Case Report Form.

Results

The demographic data

All subjects were judged to be healthy based on physical examination, medical history, vital signs and clinical laboratory test. All had negative HIV test and normal in urinary test. The mean of clinical laboratory data of all subjects is shown in Table 1. BMI of each subject was within the range of 18-25.

Pharmacokinetic parameters

The plasma rosiglitazone concentration at each sampling time up to 48 hours following a single oral dose of 8 mg the innovator's product and generic product were determined. The graphic profile curve of mean plasma rosiglitazone concentration vs. time of the two products and mean plasma rosiglitazone concentration at each blood sampling period are shown in Fig. 1 and Table 2, respectively.

The pharmacokinetic parameters for bioequivalence study including time to peak plasma rosiglitazone concentration (T_{max}), peak plasma rosiglitazone concentrations (C_{max}) and area under the plasma rosiglitazone concentration-time curve ($AUC_{0-t,}AUC_{0-inf}$) were determined. After oral single dose, mean (range) of T_{max} of generic product was 0.82 hrs (0.25-2.50 hrs) and the innovator's product was 1.02 (0.25-8.00 hrs) hrs. The mean ± SD of those parameters of generic product and the innovator's product were 796.51 ± 155.19 vs. 723.48 ± 134.69 ng/ml of C_{max}, 3.94 ± 0.80 vs. 3.87 ± 0.77 hr of $T_{½}$, 4,308.43 ±

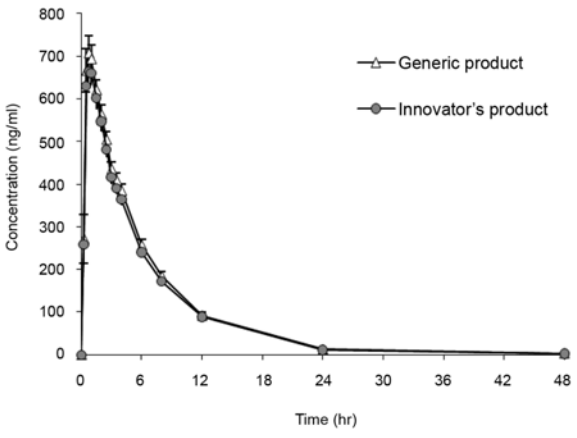

Fig. 1 Mean ± SEM plasma rosiglitazone concentration-time curve after single oral dose 8 mg of generic and the innovator's product (n = 24) SEM = Standard error of mean

Table 1. Mean clinical laboratory and demographic data of 24 subjects

Parameters	Normal values	Mean ± SD	Range
Hemoglobin (g/dl)	12-18	14.75 ± 1.18	12.8-17.1
Hematocrit (%)	37-54	43.67 ± 2.97	37.7-49.1
Glucose (mg/dl)	70-110	84.17 ± 5.88	74-93
BUN (mg/dl)	10-20	11.71 ± 3.33	2-17
Creatinine (mg/dl)	0.5-2.0	0.92 ± 0.18	0.3-1.2
SGOT (U/L)	0-38	18.17 ± 4.56	13-29
SGPT (U/L)	0-38	17.13 ± 7.39	5-35
Alkaline phosphatase (U/L)	39-117	71.71 ± 9.86	52-88
Anti HIV	Negative	Negative	Negative
Anti HBsAg	Negative	Negative	Negative
Urinalysis	Normal	Normal	Normal
Age (year)	-	20.71 ± 1.43	18-23
Body weight (kg)	-	63.72 ± 6.20	53.2-77.0
Height (cm)	-	173 ± 0.06	158-182
BMI	-	21.36 ± 1.67	18.64-24.89
Pulse rate (per min)	-	67.83 ± 5.95	60-84
Sytolic blood pressure (mmHg)	90-140	110.00 ± 7.37	100-120
Diastolic blood pressure (mmHg)	60-90	65.00 ± 7.22	50-80

SD = standard deviation

Table 2. Mean ± SD of rosiglitazone concentrations (ng/ml) in 24 subjects at each blood sampling time of generic and the innovator's product

Time after administration (hr)	Mean ± SD	
	Generic product	Innovator's product
Baseline (0)	0.00	0
0.25	272.15 ± 280.11	258.43 ± 233.61
0.5	666.42 ± 250.17	630.66 ± 198.82
0.75	707.62 ± 194.32	664.31 ± 177.47
1	693.90 ± 163.70	660.71 ± 140.79
1.5	620.94 ± 112.06	601.65 ± 125.55
2	563.66 ± 112.48	546.66 ± 111.10
2.5	504.75 ± 91.96	481.55 ± 89.85
3	435.24 ± 82.76	415.85 ± 77.23
3.5	409.27 ± 80.86	390.37 ± 68.23
4	385.00 ± 78.56	363.97 ± 68.26
6	256.84 ± 65.68	240.14 ± 59.46
8	184.16 ± 53.39	171.70 ± 57.40
12	92.14 ± 38.83	88.93 ± 51.92
24	13.05 ± 10.42	11.79 ± 12.36
48	3.68 ± 0.00	2.92 ± 0.34

1,006.28 vs. 4,135.66 ± 1,061.96 ng.hr/ml of AUC_{0-t}, 4,384.65 ± 1,035.15 vs. 4,183.87 ± 1,075.39 ng.hr/ml of AUC_{0-inf}, respectively, as shown in Table 3. By ANOVA and 90% CI analysis, the mean difference of C_{max}, AUC_{0-t} and AUC_{0-inf} (log transformed data) of generic product and the innovator's product were 98.42-122.18%, 97.28-109.66% and 97.79-110.30%, respectively, as shown in Table 3.

Adverse events

The adverse events were monitored during and after drug administration. All subjects completed in the present study without sign of hepatotoxicity or any serious adverse events from neither generic product and the innovator's product. No other adverse event had been detected in the subjects.

Discussion

The purpose of the present study was to determine the bioequivalence of rosiglitazone following an administration of 8 mg of the innovator's product and generic product. The analytical method was modified from the method of Hruska MW et al[8] and Kolte BL el al[9], using automated HPLC with fluorescence detection. The assay was practical and reliable tested by the method validation guidance of US FDA, CDER, CVM[10].

Percent accuracy at low, medium and high concentration were within the acceptance range 80-120% with %CV < 15. In terms of precision, the percentage of coefficient of variation in intra-day and inter-day assay were also within the acceptance range

Table 3. Pharmacokinetic parameters (mean ± SD) in 24 subjects following a single oral dose of Rosiglitazone 8 mg and 90% CI of the difference between generic and the innovator's product

Parameters	Mean ± SD		90% CI
	Generic product	Innovator's product	
T_{max} (hr)	0.82 ± 0.52	1.02 ± 1.50	-
C_{max} (ng/ml)	796.51 ± 155.19	723.48 ± 134.69	98.42-122.18
$T_{½}$ (hr)	3.94 ± 0.80	3.87 ± 0.77	-
AUC_{0-t} (ng.hr/ml)	4,308.43 ± 1,006.28	4,135.66 ± 1,061.96	97.28-109.66
AUC_{0-inf} (ng.hr/ml)	4,384.65 ± 1,035.15	4,183.87 ± 1,075.39	97.79-110.30

± SD = ± standard deviation
90% CI = 90% confidence interval

Table 4. Comparison of pharmacokinetic parameters (mean ± SD) of 8 mg dose rosiglitazone among Thai subjects and other countries[11]

Parameters	Mean ± SD		
	Thai (n = 24)	Saudi Arabian[11] (n = 28)	USA[12] (n=10)
T_{max} (hr)	1.02 ± 1.50	0.80 ± 0.50	2.98
C_{max} (µg/ml)	0.72 ± 0.13	0.99 ± 0.34	0.37 ± 0.10
$T_{½}$ (hr)	3.87 ± 0.77	5.00 ± 2.00	3.81 ± 0.86
AUC_{0-t} (µg hr/ml)	4.14 ± 1.06	4.76 ± 1.94	-
AUC_{0-inf} (µg hr/ml)	4.18 ± 1.08	5.08 ± 2.27	2.39 ± 0.49

(%CV < 15%). Thus, that showed valid in accuracy and precision. The standard curve covered the range of human plasma concentration of rosiglitazone dosage 8 mg followed good linearity with the correlation coefficient (R^2) closed to 1. Rosiglitazone in plasma was stable within two month long term interval or even short term stability, autosampler stability and three cycles of freeze and thaw.

The 24 male subjects enrolled in the present study were healthy. Their BMI and body weight were within the acceptable range. After treatment with generic product and the innovator's product, neither sign of hepatotoxicity nor other adverse events had been detected in all subjects. The result of mean pharmacokinetic parameters (mean ± SD) of rosiglitazone from 24 subjects including C_{max}, T_{max}, AUC_{0-t} and AUC_{0-inf} were calculated from the data of plasma rosiglitazone concentration at each time of blood collection.

T_{max} and C_{max} show the evidence involving the rate of drug absorption. AUC_{0-t} and AUC_{0-inf} are the prominent parameter indicating whole drug existing in the body. In the present study, T_{max} of rosiglitazone was rapidly absorbed at 1.0 ± 1.5 hour after a single oral administration with the C_{max} of 723.48 ± 134.69 ng/ml in Thai healthy subjects. The AUC_{0-t} and AUC_{0-inf} were 4,135.66 ± 1,061.96 and 4,183.87 ± 1,075.39 ng.hr/ml, respectively.

Previous studies from different countries including Saudi Arabia and USA. reported pharmacokinetic parameters of 8 mg dosage of rosiglitazone[11,12]. The comparison of parameters is presented in Table 4. There are some differences of T_{max}, C_{max}, $T_{½}$ and AUC in different races among Thai (Asia), Arabian and Caucasian. Time to reach peak plasma concentration (T_{max}) of the present study was slightly slower than of Saudi Arabia, but more rapid than of the USA. Maximum level of plasma concentration (C_{max}) and the extent of drug absorption into systemic circulation (AUC_{0-t} and AUC_{0-inf}) from the present study were lower than of the Saudi Arabian report but higher than of the USA report. The elimination half-life of rosiglitazone in Thai healthy subjects was 3.87 hours that showed shorter than of Arabian subjects but comparable to USA subjects. All show differences in pharmacokinetic process including absorption, metabolism and excretion among different races.

C_{max}, AUC_{0-t} and AUC_{0-inf} (log transformed data) of generic product compare to the innovator's product were not significantly different when analysis by ANOVA for two way crossover design and 90% confidence interval of C_{max}, AUC_{0-t} and AUC_{0-inf} (log transformed data) of generic product and the innovator's product are in the acceptance criteria 80-125%. These findings show the equivalence of bioavailability of generic product and the innovator's product. The result of ANOVA test for log transformed data of AUC_{0-t} and AUC_{0-inf} showed significant difference in subject effects, data not shown. Those parameters prominently represent that there were some variability factors in the presented subjects.

Conclusion

Pharmacokinetic parameters of 8 mg single oral dose of rosiglitazone were characterized in Thai male healthy subjects. These parameters in the present study were different from the previous report[11]. The 90% confidence interval for the differences of C_{max}, AUC_{0-t} and AUC_{0-inf} of generic product and the innovator's product were in the acceptance criteria 80-125%. It could be concluded that the new generic product of rosiglitazone and the innovator's product are equivalent in bioavailability.

Acknowledgement

The present study was supported by Chula-MRC Bioequivalence Center, Faculty of Medicine, Chulalongkorn University and Private sector fund.

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เภสัชจลนศาสตร์และการศึกษาชีวสมมูลของยาเม็ดรับประทานโรสิกลิตาโซน 8 มิลลิกรัมในอาสาสมัครไทยสุขภาพดี

สุพีชา วิทยเลิศปัญญา, สุมนา ชมพูทวีป, นงนุช ถาวร, วันดี เข็มศรี, นันทนา อินทนิล

ภูมิหลัง: *โรสิกลิตาโซนเป็นยาเม็ดลดระดับน้ำตาลในเลือดกลุ่ม thiazolidinediones มีข้อบ่งใช้ในการรักษาผู้ป่วยเบาหวานชนิดที่ 2 ปัจจุบันบริษัทยาในประเทศได้ผลิตยาสามัญโรสิกลิตาโซน การศึกษาทางด้านเภสัชจลนศาสตร์และชีวสมมูลของยาสามัญใหม่นี้เปรียบเทียบกับยาต้นแบบจึงจำเป็นต้องทำเพื่อยืนยันถึงคุณภาพของยา*

วัตถุประสงค์: *หาค่าทางเภสัชจลนศาสตร์ของยาโรสิกลิตาโซนในคนไทย และศึกษาชีวสมมูลของยาเม็ดรูปรับประทานโรสิกลิตาโซนขนาด 8 มิลลิกรัม ของยาสามัญใหม่เปรียบเทียบกับยาต้นแบบ*

วัสดุและวิธีการ: *ทำการศึกษาในอาสาสมัครชายไทยสุขภาพดี 24 ราย แต่ละรายจะได้รับยาเม็ดรูปรับประทานโรสิกลิตาโซนขนาด 8 มิลลิกรัม ที่ผลิตจากในประเทศและยาต้นแบบ โดยใช้รูปแบบการศึกษา แบบสุ่มสลับข้างและปกปิด เว้นระยะห่างของการให้ยาทั้งสองเป็นเวลา 2 สัปดาห์ อาสาสมัครจะถูกเจาะเลือดเป็นระยะ ๆ ที่เวลาก่อนและหลังรับประทานยาจนถึง 48 ชั่วโมง ตัวอย่างพลาสมาจะถูกวัดระดับยาโรซิกลิตาโซน ด้วยวิธีเอชพีแอลซี โดยใช้ฟลูออเรสเซนส์ตรวจวัดวิเคราะห์หาค่าทางเภสัชจลนศาสตร์โดยวิธี non compartment model ทดสอบความมีชีวสมมูลโดยวิเคราะห์ความแตกต่างของค่า $C_{max,}$ AUC_{0-t}, AUC_{0-inf} ด้วยวิธี ANOVA และเปรียบเทียบค่าเฉลี่ยที่ความเชื่อมั่น 90 เปอร์เซ็นต์*

ผลการศึกษา: *ค่า T_{max}, C_{max}, $T_{½}$, AUC_{0-t} และ AUC_{0-inf} ของยาสามัญใหม่เปรียบเทียบกับยาต้นแบบเท่ากับ 0.82 $\pm$ 0.52 และ 1.02 $\pm$ 1.50 ชั่วโมง, 796.51 $\pm$ 155.19 และ 723.48 $\pm$ 134.69 นาโนกรัมต่อมิลลิลิตร, 3.94 $\pm$ 0.80 vs. 3.87 $\pm$ 0.77 ชั่วโมง, 4,308.43 $\pm$ 1,006.28 และ 4,135.66 $\pm$ 1,061.96 นาโนกรัม.ชั่วโมงต่อมิลลิลิตร และ 4,384.65 $\pm$ 1,035.15 และ 4,183.87 $\pm$ 1,075.39 นาโนกรัม.ชั่วโมงต่อมิลลิลิตรตามลำดับ ความแตกต่างของค่าเฉลี่ยของค่า log C_{max}, AUC_{0-t} และ AUC_{0-inf} ที่ความเชื่อมั่น 90 เปอร์เซ็นต์ ของยาสามัญใหม่เปรียบเทียบกับยาต้นแบบเท่ากับ 98.42-122.18%, 97.28-109.66% และ 97.79-110.30% ตามลำดับ ซึ่งค่าที่ได้อยู่ในเกณฑ์ที่ยอมรับได้คือช่วง 80-125%*

สรุป: *พารามิเตอร์ทางเภสัชจลนศาสตร์ของยาโรสิกลิตาโซนในอาสาสมัครไทย มีอัตราการดูดซึมเร็วและค่าครึ่งชีวิตสั้นและยาโรสิกลิตาโซนทั้งสองตำรับมีชีวสมมูลกัน*